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(54) **USE OF A BLOOD-FLOW DECREASE PREVENTING AGENT IN CONJUNCTION WITH INSUFFLATING GAS**

VERWENDUNG EINES MITTELS ZUR VERHINDERUNG EINER VERRINGERUNG DES BLUTFLUSSES IN VERBINDUNG MIT EINEM INSUFFLATIONSGAS

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- **ANEMAN ANDERS ET AL: "Intestinal perfusion during pneumoperitoneum with carbon dioxide, nitrogen, and nitric oxide during laparoscopic surgery" January 2000 (2000-01), EUROPEAN JOURNAL OF SURGERY, VOL. 166, NR. 1, PAGE (S) 70-76 , XP009108375 ISSN: 1102-4151 \* the whole document \***

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**Description**Technical Field

**[0001]** This invention is directed at negating or reducing decrease in blood-flow to abdominal organs which would otherwise have decreased oxygen delivery because of being contacted with an insufflating gas, typically carbon dioxide.

Background of the Invention

**[0002]** In laparoscopic surgery or diagnosis, the insufflating gas used normally is carbon dioxide. However, the carbon dioxide pneumoperitoneum decreases blood-flow to abdominal organs, and this can result in elevated liver functions, decreased renal perfusion, hypercapnic acidosis (due to failure to remove acid from tissue because of abnormal blood-flow), and in the case of the pregnant female, impairment of blood-flow to foetus and severe hypoxemia in foetus.

**[0003]** WO 94/00180 relates to methods and devices for using nitric oxide to decrease or prevent contraction of a smooth muscle in a non-respiratory tract hollow organ which contains or is surrounded by a biological fluid other than blood, by introducing the NO into the biological fluid.

**[0004]** US 6,314,956 relates to the use of NO compounds to treat respiratory, cardiac and blood disorders by administering NO compounds directly into the lungs of a subject.

Summary of the Invention

**[0005]** One embodiment herein, denoted the first embodiment, is directed to a gaseous composition for use in negating or reducing a decrease in blood flow and/or hypoxemia in the liver, kidneys or pancreas or a foetus or placenta, in an animal having an abdominal cavity, caused by insufflation of carbon dioxide into the abdominal cavity comprising:

- a) carbon dioxide; and
- b) an agent which comprises a gas selected from the group consisting of gases having the formula  $RX-NO_y$  where R is either not present or is hydrogen or proton or  $C_1-C_7$  alkyl, X is oxygen, sulfur, nitrogen or metal selected from the group consisting of iron, copper, ruthenium and cobalt atoms or an alkyl or alkenyl or alkylthio or alkenylthio group, containing from 1 to 7 carbon atoms, and y is 1 or 2 provided that  $RX-NO_y$  is not nitrous oxide, and NOQ or QNO where Q is halogen or hydrogen, NOQ or QNO generating agents, alkyl nitrososulfonates where the alkyl group contains from 1 to 10 carbon atoms, thionitrosochloronitrite, thionitrosodinitrite,  $RSNO_2$  where R is an alkyl group containing from 1 to 10 carbon atoms

or is a small peptide, nitrosourea,  $NO_2$ ,  $N_2O_3$  and carbon monoxide;

wherein the composition is administered directly into the abdominal cavity.

**[0006]** The agent is preferably an alkyl nitrite such as ethyl nitrite. The amount of agent preferably ranges from 1 to 1,000 ppm, e.g., 50 to 200 ppm ethyl nitrite. Gas insufflation into the peritoneum also impairs fetal blood flow and ethyl nitrite or other vasodilating gas can diffuse into the blood to improve fetal blood flow and hypoxemia.

**[0007]** Pneumoperitoneum also impairs pulmonary function and raises blood pressure and ethyl nitrite has been shown to improve pulmonary function and can lower blood pressure.

**[0008]** The first embodiment provides a way to prevent or reverse with a drug a complication of a laparoscopic procedure analogous to giving a patient a drug to raise blood pressure if blood pressure drops during surgery. The medicament of the first embodiment treats a complication of laparoscopic surgery or diagnosis.

**[0009]** The medicament of the first embodiment is used in the treatment of mammals, including humans.

**[0010]** Another embodiment herein, denoted the second embodiment, is directed to a gas for use in a laparoscopic procedure consisting of an insufflating gas which is carbon dioxide and an agent which prevents a decreased blood flow and/or hypoxemia to the liver, kidneys or pancreas or a foetus or placenta, wherein the agent is as described above for the first embodiment.

**[0011]** A third embodiment is directed to a gas for use in a laparoscopic procedure consisting of a gas for use in a laparoscopic procedure consisting of insufflating gas which is carbon dioxide and an agent which prevents a decrease in blood flow and/or hypoxemia to the liver, kidneys or pancreas or a foetus or placenta, in an amount ranging from 1 to 1,000 ppm, wherein the agent is ethyl nitrite.

Brief Description of the Drawings**[0012]**

Fig. 1 is a graph of Time (hours) versus Doppler Flow Units and shows results for effect on liver in respect to blood-flow in liver, of carbon dioxide gas insufflation (15 mm Hg (2 kPa) for 1 hour) as determined in the experiment of Example 1 and represents the current state-of-the-art.

Fig. 2 is a graph of Time (hours) versus Doppler Flow Units and shows results for effect on liver in respect to blood-flow in liver, of insufflation with carbon dioxide gas containing 100 ppm ethyl nitrite as determined in the experiment of Example I and represents the invention.

Fig. 3 depicts graphs of relative blood-flow compared

to baseline and shows effect on liver of carbon dioxide alone and of gas consisting of carbon dioxide and 100 ppm ethyl nitrite and shows results during insufflation and two hours post insufflation as determined in the experiment of Example I. In Fig. 3, CO<sub>2</sub> means CO<sub>2</sub> and E-NO means ethyl nitrite.

#### Detailed Description

**[0013]** We turn now to the embodiment herein, denoted the first embodiment herein, which is directed to a gaseous composition for use in negating or reducing decrease in blood-flow and/or hypoxemia in the liver, kidneys or pancreas or a foetus or placenta in an animal having an abdominal cavity, caused by insufflation of carbon dioxide into the abdominal cavity comprising carbon dioxide; and an agent which comprises a gas selected from the group consisting of gases having the formula RX-NO<sub>y</sub> where R is either not present or is hydrogen or proton or C<sub>1</sub>-C<sub>7</sub> -alkyl, X is oxygen, sulfur, nitrogen or metal selected from the group consisting of iron, copper, ruthenium and cobalt atoms or an alkyl or alkenyl or alkylthio or alkenylthio group, containing from 1 to 7 carbon atoms, and y is 1 or 2 provided that RX--NO<sub>y</sub> is not nitrous oxide, and NO<sub>Q</sub> or NO where Q is halogen or hydrogen, NO<sub>Q</sub> or QNO generating agents, alkyl nitroso-sulfonates where the alkyl group contains from 1 to 10 carbon atoms, thionitrosochloronitrite, thionyl dinitrite, RSNO<sub>2</sub> where R is an alkyl group containing from 1 to 10 carbon atoms or is a small peptide, nitroso-urea, NO<sub>2</sub>, N<sub>2</sub>O<sub>3</sub> and carbon monoxide; wherein the composition is administered directly into the abdominal cavity.

**[0014]** The medicament is used in laparoscopic surgery, or in a laparoscopic diagnostic procedure, as a therapeutic agent.

**[0015]** Laparoscopic surgery allows surgery with minimal tissue injury and relies on a miniature video camera and surgical instruments inserted into the abdominal cavity usually through a small cut in the umbilicus. After an initial cut, a needle adapted to deliver insufflating gas is inserted. Then the insufflating gas is delivered into the abdominal cavity to expand the abdominal cavity to enable better visualization and greater workspace. The pressure resulting from the gas delivery normally should not exceed 15 mm Hg (2kPa). The insufflating gas conventionally consists of carbon dioxide. After sufficient expansion is obtained, a trocar is inserted through the umbilical cut. This is used for access to insert the miniature video camera and surgical instruments. The video camera provides high resolution visualization and allows proper manipulation of the surgical instruments to carry out surgery effectively.

**[0016]** Diagnostic laparoscopy corresponds to laparoscopic surgery so far as initial cut and insertion of insufflating gas is concerned but the video camera is inserted to obtain diagnosis and surgery is not carried out.

**[0017]** Some texts available from Amazon.com in

June, 2001 on laparoscopy include the following: Ballantyne, G. H., Atlas of Laparoscopic Surgery; Eubanks, S. (ed), et al., Mastery of Endoscopic and Laparoscopic Surgery; Pappas, T. N., Atlas of Laparoscopic Surgery; Beshoff, J. T., et al., Atlas of Laparoscopic Retroperitoneal Surgery; MacIntyre, I. M. C., Practical Laparoscopic Surgery for General Surgeons (8/94).

**[0018]** Surgery and diagnosis can be effected on abdominal organs within the peritoneum, e.g., on liver, or on opening of the peritoneum on retroperitoneal organs, e.g., kidneys and pancreas.

**[0019]** When the abdominal organs that are the subject of the laparoscopic procedure, are within the peritoneum, e.g., liver, then organs within the peritoneum would otherwise have decreased blood-flow and are beneficially acted by the invention herein. When the abdominal organs that are the subject of the laparoscopic procedure are retroperitoneal, then the retroperitoneal organs would otherwise have decreased blood-flow and serum creatine increases associated with kidney dysfunction and are beneficially aided by the invention herein.

**[0020]** The application of the first embodiment of the instant invention to laparoscopic surgery can be described as follows: In laparoscopic surgery, wherein an insufflating gas is delivered into the abdominal cavity to enable better visualization and greater work space, the agent in an effective amount contacts the abdominal organs contacted with the insufflating gas.

**[0021]** The application of the first embodiment of the instant invention to a laparoscopic diagnostic procedure can be described as follows: In laparoscopic diagnosis, wherein an insufflating gas is delivered into the abdominal cavity to enable better visualization, the agent in an effective amount contacts the abdominal organs contacted with the insufflating gas.

**[0022]** The agents may cause blood vessel dilation or that increase blood-flow by decreasing platelets or by decreasing neutrophil or red blood plugging of vessels or by decreasing blood viscosity.

**[0023]** We turn now to use of the gas. As in the case of conventional laparoscopy, the pressure resulting from gas delivery should normally not exceed 15 mm Hg (2 kPa). Within this framework, the amount of gas should be sufficient to allow sufficient visualization and work space for laparoscopy.

**[0024]** The gas can be delivered using a CO<sub>2</sub> insufflator equipped with a pressure regulator.

**[0025]** As indicated above, the gas consists essentially of an agent in an effective amount and the insufflating gas.

**[0026]** When the agent is administered as part of a gas, it must normally be a gas under the conditions of administration or must be converted to a gas for administration. The agents should not have a boiling point such that the temperature required to maintain them as gases in diluted form, i.e., in combination with insufflating gas, would harm an abdominal organ and preferably should not condense in the abdominal cavity.

**[0027]** The agents which are administered as part of a gas have the formula  $RX-NO_y$  where R is either not present or is hydrogen/proton or C<sub>1</sub>-C<sub>7</sub>-alkyl and X is oxygen, sulfur, nitrogen or metal selected, for example, from the group consisting of iron, copper, ruthenium and cobalt atoms or an alkyl or alkenyl or alkylthio or alkenylthio group containing from 1 to 7, e.g., 1 to 6, carbon atoms which is straight chain or branched, or CF<sub>3</sub>- or CF<sub>3</sub>S-, and y is 1 or 2, excluding nitrous oxide. Specific treating agents of the  $RX-NO_y$  class include, for example, ethyl nitrite (which is the very preferred agent for use in the embodiments herein and is used in examples herein), methyl nitrite, tert-butyl nitrite, isoamyl nitrite, trifluoronitrosomethane (CF<sub>3</sub>NO), CF<sub>3</sub>SNO, CH<sub>3</sub>SNO, CH<sub>2</sub>=CHSNO, CH<sub>2</sub>=CHCH<sub>2</sub>SNO, ONSCH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>SNO and CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>SNO. Alkyl nitrites can be prepared as described in Landscheidt et al. US. Patent No. 5,412,147. Ethyl nitrite is available commercially, e.g., diluted in ethanol. CF<sub>3</sub>NO is a commercial product or can be made by treatment of CF<sub>3</sub>I with NO<sup>-</sup> as described in J. Phys. Chem. 100, 10641 (1996). Aliphatic thionitrites, i.e., compounds of the form RSNO where R describes an alkyl or alkenyl or hydrogen moiety, can be prepared by treatment of the corresponding thiol with a source of NO<sup>+</sup> including, but not limited to, one or more of the following: *tert*-butyl nitrite, ethyl nitrite, nitrosonium tetrafluoroborate (NOBF<sub>4</sub>), nitrosonium perchlorate (NOClO<sub>4</sub>), nitrosonium hydrogen sulfate (NOHSO<sub>4</sub>), nitrosonium hydrogen phosphate (NOH<sub>2</sub>PO<sub>4</sub>), or HCl-acidified solutions of sodium nitrite.

**[0028]** Other agents for use in the embodiments herein, which are normally gases or which can be converted into a gas for administration, include NOQ or QNO where Q is halogen, e.g., Cl, Br or F, or hydrogen or NOQ or QNO generating agents, alkyl nitrososulfonates (RSO<sub>2</sub>NO) where the alkyl group contains from 1 to 10 carbon atoms, thionitrosochloronitrite (SOClONO), thionitrosodinitrite (SO(ONO)<sub>2</sub>) and alkyl (including small peptides) thionitrites (RSNO<sub>2</sub>) wherein the alkyl group contains from 1 to 10 carbon atoms or is a small peptide, and nitrosourea.

**[0029]** Other agents for use in the embodiments herein, which are normally gases, are nitric oxide (NO), NO<sub>2</sub> and N<sub>2</sub>O<sub>3</sub>.

**[0030]** Still another agent for use in the embodiments herein, which is normally a gas, is carbon monoxide.

**[0031]** As indicated above, the agent for use in the embodiments herein is used in a therapeutically effective amount. This is an amount that negates or reduces the blood-flow to abdominal organ decrease and relieves or reduces the resulting hypoxemia that without the instant invention would occur, to extent of effecting blood-flow that is at least 5% of that present in the organ if it were not contacted with insufflating agent, typically carbon dioxide, as measured by Doppler or tissue oxygenation.

**[0032]** The agent typically constitutes from 1 to 1,000 ppm, e.g., 50 to 200 ppm, of the gas consisting essentially of insufflating gas, typically carbon dioxide, and agent.

**[0033]** The agent can be admixed with carbon dioxide or other insufflating gas to provide a gas for administration, e.g., by conventional gas blending methods.

**[0034]** We turn now to the second embodiment herein.

5 The agents are those described above in conjunction with the first embodiment herein. The effective amount is that described above in conjunction with the first embodiment herein. Very preferably, the gas consists essentially of carbon dioxide and from 1 to 1,000 ppm, e.g., 50 to 200 ppm, agent, very preferably ethyl nitrite, very preferably ethyl nitrite Admixture of the carbon dioxide and agent can be effected as described for the first embodiment.

10 **[0035]** The invention herein supported by or illustrated by the following working examples.

15

#### Example 1

**[0036]** Ten adult pigs were anesthetized at time zero using halothane anesthetic. A small cut was made in the abdomen to allow access inside the peritoneum. In the case of one group of five pigs, denoted group A, an insufflating needle was inserted, and starting at time 1 hour and 48 minutes, an insufflating gas consisting of carbon dioxide was delivered into the abdominal cavity to standard operating pressure (of 15 mm Hg; 2 kPa) and the insufflating gas was maintained in the abdominal cavity for 1 hour whereupon the insufflating gas was removed by suction. In the case of another group of five pigs, denoted group B, an insufflating needle was inserted, and starting at time 1 hour and 35 minutes, an insufflating gas consisting of carbon dioxide and 100 ppm ethyl nitrite was delivered to the abdominal cavity to standard operating pressure and the insufflating gas was maintained in the abdominal cavity for about 1 1/5 hour whereupon the insufflating gas was removed by suction. In both cases, blood-flow in liver was monitored by a laser Doppler flow method (a standard method where ultrasonic waves are projected at flowing blood and bounce back) whereby blood-flow is determined starting at time 5 minutes after time zero in the case of group A, and starting at about time 20 minutes after time zero in the case of group B and continuing until 2 hours after insufflating gas was removed. Results are shown in FIGS. 1-3. In FIGS. 1 and 2, the Doppler Flow Units are arbitrary units. In FIG. 3, the term "Relative Flow" means relative blood-flow in liver compared to baseline. FIG. 1 shows blood-flow results (flow in liver) for group A (carbon dioxide only). FIG. 1 illustrates that carbon dioxide pneumoperitoneum produces a decrease in blood-flow to the liver, which was sustained even after the procedure was completed. FIG. 2 shows blood-flow results (flow in liver) for group B (carbon dioxide together with 100 ppm ethyl nitrite). FIG. 2 shows that ethyl nitrite protects against carbon dioxide induced decline in liver perfusion. FIG. 3 shows average values of blood-flow in liver for "Liver Insufflation," that is while insufflating gas is present, and "Liver Post-Insufflation," that is 2 hours after insufflating gas is removed. FIG. 3 shows about 70% more blood-flow in the ethyl

nitrite case during insufflation and about 40% more blood-flow in the ethyl nitrite case 2 hours post-insufflation. The same protection by ethyl nitrite against renal dysfunction is predicted where the peritoneum is opened.

#### Example II

**[0037]** A 23-year-old black female, 32 weeks pregnant, undergoes laparoscopic evaluation for right lower quadrant pain. Thirty minutes into the procedure, fetal PO<sub>2</sub>, measured by an electrode placed on the head, is 7 mm Hg (0.9 kPa). 100 ppm ethyl nitrite is added to the carbon dioxide insufflating gas, and the fetal PO<sub>2</sub> increases to 25 mm Hg (3.3 kPa).

#### Example III

**[0038]** A 70-year-old male undergoes laparoscopic cholecystectomy. One hour into the procedure, liver function tests start to rise and the patient complains of abdominal pain suggestive of intestinal ischemia. Ethyl nitrite 100 ppm is added to the insufflating gas with resolution of abdominal pain.

#### Example IV

**[0039]** A 55-year-old woman with renal artery stenosis undergoes laparoscopy appendectomy and diagnostic evaluation of a renal mass. Because of concerns regarding decreased renal perfusion, 100 ppm ethyl nitrite is added to insufflating gas and protects against decrease in blood-flow.

#### Example V

**[0040]** A sixty-year-old white female undergoes laparoscopic appendectomy. Because of concerns of impaired renal function, pulmonary function and hypertension, nitroglycerin (3 cc of 100 micromolar) is nebulized into the abdominal cavity. Blood pressure increases are prevented and pulmonary and renal functions are kept stable.

#### **Claims**

1. A gaseous composition for use in negating or reducing a decrease in blood flow and/or hypoxemia in the liver, kidneys or pancreas or a foetus or placenta, in an animal having an abdominal cavity, caused by insufflation of carbon dioxide into the abdominal cavity comprising:
  - a) carbon dioxide; and
  - b) an agent which comprises a gas selected from the group consisting of gases having the formula RX--NO<sub>y</sub> where R is either not present or is hydrogen or proton or C<sub>1</sub>-C<sub>7</sub>-alkyl, X is oxygen,

sulfur, nitrogen or metal selected from the group consisting of iron, copper, ruthenium and cobalt atoms or an alkyl or alkenyl or alkylthio or alkenylthio group, containing from 1 to 7 carbon atoms, and y is 1 or 2 provided that RX--NO<sub>y</sub> is not nitrous oxide, and NOQ or QNO where Q is halogen or hydrogen, NOQ or QNO generating agents, alkyl nitrososulfates where the alkyl group contains from 1 to 10 carbon atoms, thionitrosochloronitrite, thionyl dinitrite, RSNO<sub>2</sub> where R is an alkyl group containing from 1 to 10 carbon atoms or is a small peptide, nitrosourea, NO<sub>2</sub>, N<sub>2</sub>O<sub>3</sub> and carbon monoxide;

wherein the composition is administered directly into the abdominal cavity.

2. The composition of claim 1, wherein the amount of the agent ranges from 1 to 1,000 ppm.
3. The composition of claim 1, wherein the agent is an alkyl nitrite.
4. The composition of claim 3, wherein the alkyl nitrite is ethyl nitrite.
5. The composition of claim 4, wherein the therapeutically effective amount of ethyl nitrite ranges from 50 to 200 ppm.
6. Use of a gaseous composition comprising carbon dioxide and an agent in the manufacture of a medicament to negate or reduce a decrease in blood flow and/or hypoxemia to the liver, kidneys or pancreas or a foetus or placenta, in an animal having an abdominal cavity, caused by insufflation of carbon dioxide into the abdominal cavity, wherein the agent is a gas selected from the group consisting of gases having the formula RX--NO<sub>y</sub> where R is either not present or is hydrogen or proton or C<sub>1</sub>-C<sub>7</sub>-alkyl, X is oxygen, sulfur, nitrogen or metal selected from the group consisting of iron, copper, ruthenium and cobalt atoms or an alkyl or alkenyl or alkylthio or alkenylthio group, containing from 1 to 7 carbon atoms, and y is 1 or 2 provided that RX--NO<sub>y</sub> is not nitrous oxide, and NOQ or QNO where Q is halogen or hydrogen, NOQ or QNO generating agents, alkyl nitrososulfates where the alkyl group contains from 1 to 10 carbon atoms, thionitrosochloronitrite, thionyl dinitrite, RSNO<sub>2</sub> where R is an alkyl group containing from 1 to 10 carbon atoms or is a small peptide, nitrosourea, NO<sub>2</sub>, N<sub>2</sub>O<sub>3</sub> and carbon monoxide, wherein the medicament is administered directly into the abdominal cavity.
7. The use of claim 6, wherein the amount of the agent ranges from 1 to 1,000 ppm.

8. Use according to claim 6, wherein the agent is an alkyl nitrite.
9. Use according to claim 8, wherein the alkyl nitrite is ethyl nitrite.
10. Use according to claim 9, wherein the therapeutically effective amount of ethyl nitrite ranges from 50 to 200 ppm.
11. A gas for use in a laparoscopic procedure consisting of an insufflating gas which is carbon dioxide and an agent which prevents a decreased blood flow and/or hypoxemia to the liver, kidneys or pancreas or a foetus or placenta, wherein the agent is a gas selected from the group consisting of gases having the formula  $RX-NO_y$  where R is either not present or is hydrogen or proton or  $C_1-C_7$ -alkyl, X is oxygen, sulfur, nitrogen or metal selected from the group consisting of iron, copper, ruthenium and cobalt atoms or an alkyl or alkenyl or alkylthio or alkenylthio group, containing from 1 to 7 carbon atoms, and y is 1 or 2 provided that  $RX-NO_y$  is not nitrous oxide, and NOQ or QNO where Q is halogen or hydrogen, NOQ or QNO generating agents, alkyl nitrososulfonates where the alkyl group contains from 1 to 10 carbon atoms, thionitrosochloronitrite, thionyl dinitrite,  $RSNO_2$  where R is an alkyl group containing from 1 to 10 carbon atoms or is a small peptide, nitroso urea,  $NO_2$ ,  $N_2O_3$  and carbon monoxide.
12. The gas of claim 11, wherein the amount of the agent ranges from 1 to 1.000ppm,
13. The gas of claim 11, wherein the agent is an alkyl nitrite,
14. The gas of claim 13, where the alkyl nitrite is ethyl nitrite.
15. A gas for use in a laparoscopic procedure consisting of insufflating gas which is carbon dioxide and an agent which prevents a decrease in blood flow and/or hypoxamin to the liver, kidneys or pancreas or a foetus or placenta, in an amount ranging from 1 to 1,000 ppm, wherein the agent is ethyl nitrite.
16. The gas of claim 15, containing 50 to 200 ppm ethyl nitrite,

### Patentansprüche

1. Gasförmige Zusammensetzung zur Verwendung zum Verhindern oder Senken einer Verminderung des Blutstroms und/oder von Hypoxämie in der Leber, den Nieren oder der Bauchspeicheldrüse, oder eines Fötus oder einer Plazenta in einem eine

Bauchhöhle aufweisenden Tier, die durch eine Insufflation von Kohlendioxid in die Bauchhöhle verursacht worden ist oder sind, umfassend:

- a) Kohlendioxid und  
 b) ein Mittel, das ein Gas umfasst, das aus der Gruppe, bestehend aus Gasen mit der Formel  $RX-NO_y$ , wobei R entweder nicht vorliegt oder Wasserstoff oder ein Proton oder  $C_1-C_7$ -Alkyl ist, X Sauerstoff, Schwefel, Stickstoff oder ein Metall, das aus der Gruppe, bestehend aus Eisen-, Kupfer-, Ruthenium- und Kobaltatomen, ausgewählt ist, oder eine Alkyl- oder Alkenyl- oder Alkylthio- oder Alkenylthiogruppe, die 1 bis 7 Kohlenstoffatome enthält, ist, und y 1 oder 2 ist, mit der Maßgabe, dass  $RX-NO_y$  nicht Distickstoffmonoxid ist, und NOQ oder QNO, wobei Q Halogen oder Wasserstoff ist, NOQ- oder QNO-erzeugenden Mitteln, Alkylnitrososulfonaten, wobei die Alkylgruppe 1 bis 10 Kohlenstoffatome enthält, Thionitrosochloronitrit, Thionyl dinitrit,  $RSNO_2$ , wobei R eine Alkylgruppe, die 1 bis 10 Kohlenstoffatome enthält, oder ein kleines Peptid ist, Nitrosoharnstoff,  $NO_2$ ,  $N_2O_3$  und Kohlenmonoxid, ausgewählt ist,

wobei die Zusammensetzung direkt in die Bauchhöhle injiziert wird.

2. Zusammensetzung nach Anspruch 1, bei der die Menge des Mittels im Bereich von 1 bis 1000 ppm liegt.
3. Zusammensetzung nach Anspruch 1, bei der das Mittel ein Alkylnitrit ist.
4. Zusammensetzung nach Anspruch 3, bei der das Alkylnitrit Ethylnitrit ist.
5. Zusammensetzung nach Anspruch 4, bei der die therapeutisch wirksame Menge von Ethylnitrit im Bereich von 50 bis 200 ppm liegt.
6. Verwendung einer gasförmigen Zusammensetzung, die Kohlendioxid und ein Mittel umfasst, zur Herstellung eines Medikaments zum Verhindern oder Senken einer Verminderung des Blutstroms und/oder von Hypoxämie zu der Leber, den Nieren oder der Bauchspeicheldrüse, oder einem Fötus oder einer Plazenta in einem eine Bauchhöhle aufweisenden Tier, die durch eine Insufflation von Kohlendioxid in die Bauchhöhle verursacht worden ist oder sind, wobei das Mittel ein Gas ist, das aus der Gruppe, bestehend aus Gasen mit der Formel  $RX-NO_y$  wobei R entweder nicht vorliegt oder Wasserstoff oder ein Proton oder  $C_1-C_7$ -Alkyl ist, X Sauerstoff, Schwefel, Stickstoff oder ein Metall, das aus der Gruppe, bestehend aus Eisen-, Kupfer-, Ruthenium- und Ko-

- baltatomen, ausgewählt ist, oder eine Alkyl- oder Alkenyl- oder Alkylthio- oder Alkenylthiogruppe, die 1 bis 7 Kohlenstoffatome enthält, ist, und y 1 oder 2 ist, mit der Maßgabe, dass  $RX-NO_y$  nicht Distickstoffmonoxid ist, und NOQ oder QNO, wobei Q Halogen oder Wasserstoff ist, NOQ- oder QNO-erzeugenden Mitteln, Alkylnitrososulfinate, wobei die Alkylgruppe 1 bis 10 Kohlenstoffatome enthält, Thionitrosochlornitrit, Thionyldinitrit,  $RSNO_2$ , wobei R eine Alkylgruppe, die 1 bis 10 Kohlenstoffatome enthält, oder ein kleines Peptid ist, Nitrosoharnstoff,  $NO_2$ ,  $N_2O_3$  und Kohlenmonoxid, ausgewählt ist, wobei das Medikament direkt in die Bauchhöhle injiziert wird.
7. Verwendung nach Anspruch 6, bei der die Menge des Mittels im Bereich von 1 bis 1000ppm liegt.
8. Verwendung nach Anspruch 6, bei der das Mittel ein Alkylnitrit ist.
9. Verwendung nach Anspruch 8, bei der das Alkylnitrit Ethylnitrit ist.
10. Verwendung nach Anspruch 9, bei der die therapeutisch wirksame Menge von Ethylnitrit im Bereich von 50 bis 200 ppm liegt.
11. Gas zur Verwendung in einem laparoskopischen Verfahren, bestehend aus einem Insufflationsgas, das Kohlendioxid ist, und einem Mittel, das einen verminderten Blutstrom und/oder eine Hypoxämie zu der Leber, den Nieren oder der Bauchspeicheldrüse, oder einem Fötus oder einer Plazenta verhindert, wobei das Mittel ein Gas ist, das aus der Gruppe, bestehend aus Gasen mit der Formel  $RX-NO_y$ , wobei R entweder nicht vorliegt oder Wasserstoff oder ein Proton oder  $C_1-C_7$ -Alkyl ist, X Sauerstoff, Schwefel, Stickstoff oder ein Metall, das aus der Gruppe, bestehend aus Eisen-, Kupfer-, Ruthenium- und Kobaltatomen, ausgewählt ist, oder eine Alkyl- oder Alkenyl- oder Alkylthio- oder Alkenylthiogruppe, die 1 bis 7 Kohlenstoffatome enthält, ist, und y 1 oder 2 ist, mit der Maßgabe, dass  $RX-NO_y$  nicht Distickstoffmonoxid ist, und NOQ oder QNO, wobei Halogen oder Wasserstoff ist, NOQ- oder QNO-erzeugenden Mitteln, Alkylnitrososulfinate, wobei die Alkylgruppe 1 bis 10 Kohlenstoffatome enthält, Thionitrosochlornitrit, Thionyldinitrit,  $RSNO_2$ , wobei R eine Alkylgruppe, die 1 bis 10 Kohlenstoffatome enthält, oder ein kleines Peptid ist, Nitrosoharnstoff,  $NO_2$ ,  $N_2O_3$  und Kohlenmonoxid, ausgewählt ist.
12. Gas nach Anspruch 11, bei dem die Menge des Mittels im Bereich von 1 bis 1000 ppm liegt.
13. Gas nach Anspruch 11, bei dem das Mittel ein Alkylnitrit ist.
14. Gas nach Anspruch 13, bei dem das Alkylnitrit Ethylnitrit ist.
15. Gas zur Verwendung in einem laparoskopischen Verfahren, bestehend aus einem Insufflationsgas, das Kohlendioxid ist, und einem Mittel, das einen verminderten Blutstrom und/oder eine Hypoxämie zu der Leber, den Nieren oder der Bauchspeicheldrüse, oder einem Fötus oder einer Plazenta verhindert, in einer Menge im Bereich von 1 bis 1000 ppm, wobei das Mittel Ethylnitrit ist.
16. Gas nach Anspruch 15, das 50 bis 200 ppm Ethylnitrit enthält.

### Revendications

1. Composition gazeuse pour utilisation dans l'annulation ou la réduction d'une diminution du flux sanguin et/ou d'une hypoxémie dans le foie, les reins ou le pancréas ou un foetus ou le placenta, chez un animal doté d'une cavité abdominale, en résultat d'une insufflation de dioxyde de carbone dans la cavité abdominale, comprenant :

- a) du dioxyde de carbone ; et  
 b) un agent qui comprend un gaz choisi dans l'ensemble constitué par les gaz de formule  $RX-NO_y$ , dans laquelle R est absent ou est l'hydrogène ou un proton ou un alkyle en  $C_1$  à  $C_7$ , X est l'oxygène, le soufre, l'azote ou un métal choisi dans l'ensemble constitué par les atomes de fer, de cuivre, de ruthénium et de cobalt, ou un groupe alkyle ou alcényle ou alkylthio ou alcénylthio, contenant de 1 à 7 atomes de carbone, et y vaut 1 ou 2, à la condition que  $RX-NO_y$  ne soit pas l'oxyde nitreux, et NOQ ou QNO où Q est une halogène ou l'hydrogène, les agents générateurs de NOQ ou QNO, les nitrososulfinate d'alkyle où le groupe alkyle contient de 1 à 10 atomes de carbone, le thionitrosochloronitrite, le dinitrite de thionyle,  $RSNO_2$  où R est un groupe alkyle contenant de 1 à 10 atomes de carbone ou est un petit peptide, la nitrosourée,  $NO_2$ ,  $N_2O_3$  et le monoxyde de carbone ;

laquelle composition est administrée directement dans la cavité abdominale.

2. Composition selon la revendication 1, dans laquelle la quantité de l'agent est située dans la plage allant de 1 à 1000 ppm.
3. Composition selon la revendication 1, dans laquelle l'agent est un nitrite d'alkyle.
4. Composition selon la revendication 3, dans laquelle

le nitrite d'alkyle est le nitrite d'éthyle.

5. Composition selon la revendication 4, dans laquelle la quantité efficace, du point de vue thérapeutique, du nitrite d'éthyle, est située dans la plage allant de 50 à 200 ppm. 5
6. Utilisation d'une composition gazeuse contenant du dioxyde de carbone et un agent dans la fabrication d'un médicament pour annuler ou réduire une diminution du flux sanguin et/ou une hypoxémie dans le foie, les reins ou le pancréas ou un fœtus ou le placenta, chez un animal doté d'une cavité abdominale, en résultat d'une insufflation de dioxyde de carbone dans la cavité abdominale, dans laquelle l'agent est un gaz choisi dans l'ensemble constitué par les gaz de formule  $RX-NO_y$ , dans laquelle R est absent ou est l'hydrogène ou un proton ou un alkyle en  $C_1$  à  $C_7$ , X est l'oxygène, le soufre, l'azote ou un métal choisi dans l'ensemble constitué par les atomes de fer, de cuivre, de ruthénium et de cobalt, ou une groupe alkyle ou alcényle ou alkylthio ou alcénylthio, contenant de 1 à 7 atomes de carbone, et y vaut 1 ou 2, à la condition que  $RX-NO_y$  ne soit pas l'oxyde nitreux, et NOQ ou QNO où Q est un halogène ou l'hydrogène, les agents générateurs de NOQ ou QNO, les nitrososulfates d'alkyle où le groupe alkyle contient de 1 à 10 atomes de carbone, le thionitrosochloronitrite, le dinitrite de thionyle,  $RSNO_2$  où R est un groupe alkyle contenant de 1 à 10 atomes de carbone ou est un petit peptide, la nitrosourée,  $NO_2$ ,  $N_2O_3$  et le monoxyde de carbone. 10  
15  
20  
25  
30
7. Utilisation selon la revendication 6, dans laquelle la quantité de l'agent est située dans la plage allant de 1 à 1000 ppm. 35
8. Composition selon la revendication 6, dans laquelle l'agent est un nitrite d'alkyle. 40
9. Composition selon la revendication 8, dans laquelle le nitrite d'alkyle est le nitrite d'éthyle. 45
10. Composition selon la revendication 9, dans laquelle la quantité efficace, du point de vue thérapeutique, du nitrite d'éthyle, est située dans la plage allant de 50 à 200 ppm. 50
11. Gaz pour utilisation dans une procédure laparoscopique consistant à insuffler un gaz qui empêche une diminution du flux sanguin et/ou une hypoxémie dans le foie, les reins ou le pancréas ou un fœtus ou le placenta, dans lequel l'agent est un gaz choisi dans l'ensemble constitué par les gaz de formule  $RX-NO_y$ , dans laquelle R est absent ou est l'hydrogène ou un proton ou un alkyle en  $C_1$  à  $C_7$ , X est l'oxygène, le soufre, l'azote ou un métal choisi dans l'ensemble constitué par les atomes de fer, de cuivre, de ruthénium et de cobalt, ou un groupe alkyle ou alcényle ou alkylthio ou alcénylthio, contenant de 1 à 7 atomes de carbone, et y vaut 1 ou 2, à la condition que  $RX-NO_y$  ne soit pas l'oxyde nitreux, et NOQ ou QNO où Q est un halogène ou l'hydrogène, les agents générateurs de NOQ ou QNO, les nitrososulfates d'alkyle où le groupe alkyle contient de 1 à 10 atomes de carbone, le thionitrosochloronitrite, le dinitrite de thionyle,  $RSNO_2$  où R est un groupe alkyle contenant de 1 à 10 atomes de carbone ou est un petit peptide, la nitrosourée,  $NO_2$ ,  $N_2O_3$  et le monoxyde de carbone. 55
12. Gaz selon la revendication 11, dans lequel la quantité de l'agent est située dans la plage allant de 1 à 1000 ppm. 60
13. Gaz selon la revendication 11, dans lequel l'agent est un nitrite d'alkyle. 65
14. Gaz selon la revendication 13, dans lequel le nitrite d'alkyle est le nitrite d'éthyle. 70
15. Gaz pour utilisation dans une procédure laparoscopique consistant à insuffler un gaz qui empêche une diminution du flux sanguin et/ou une hypoxémie au foie, aux reins ou au pancréas ou à un fœtus ou au placenta, en une quantité située dans la plage allant de 1 à 1000 ppm, dans lequel l'agent est le nitrite d'éthyle. 75
16. Gaz selon la revendication 15, contenant 50 à 200 ppm de nitrite d'éthyle. 80

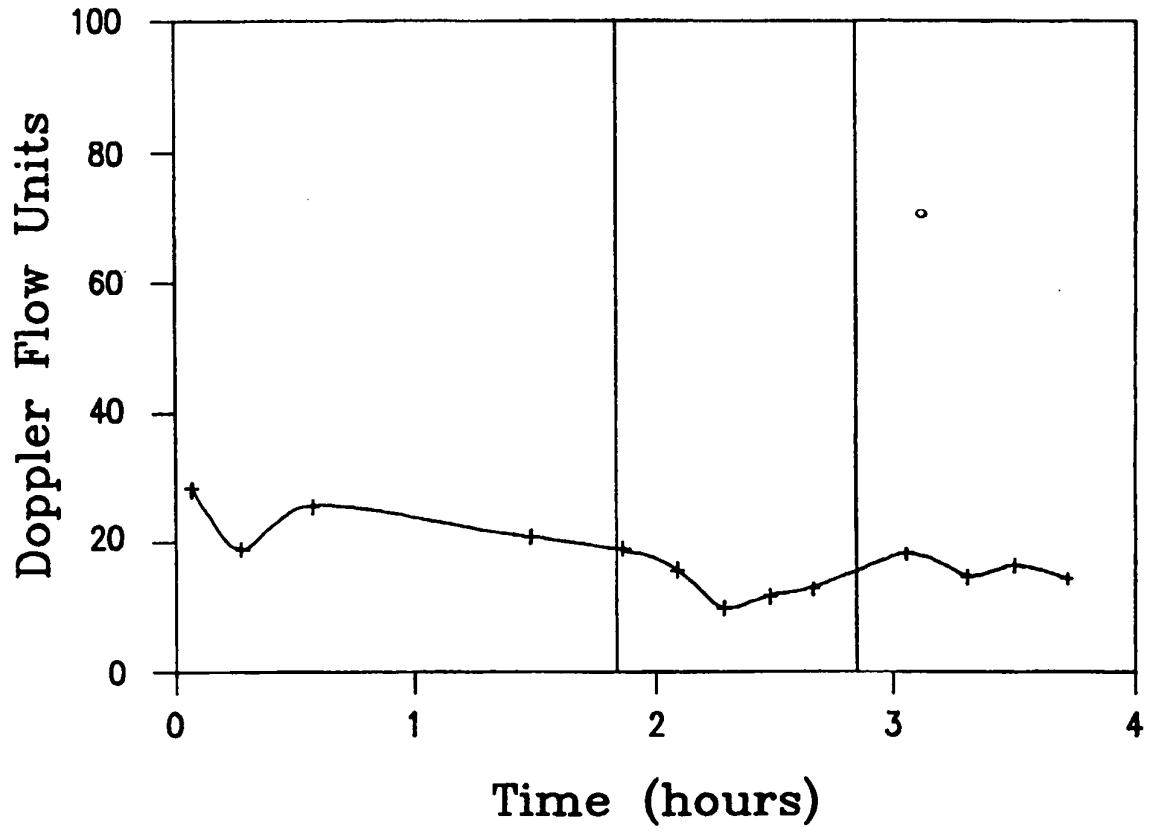


FIG. 1

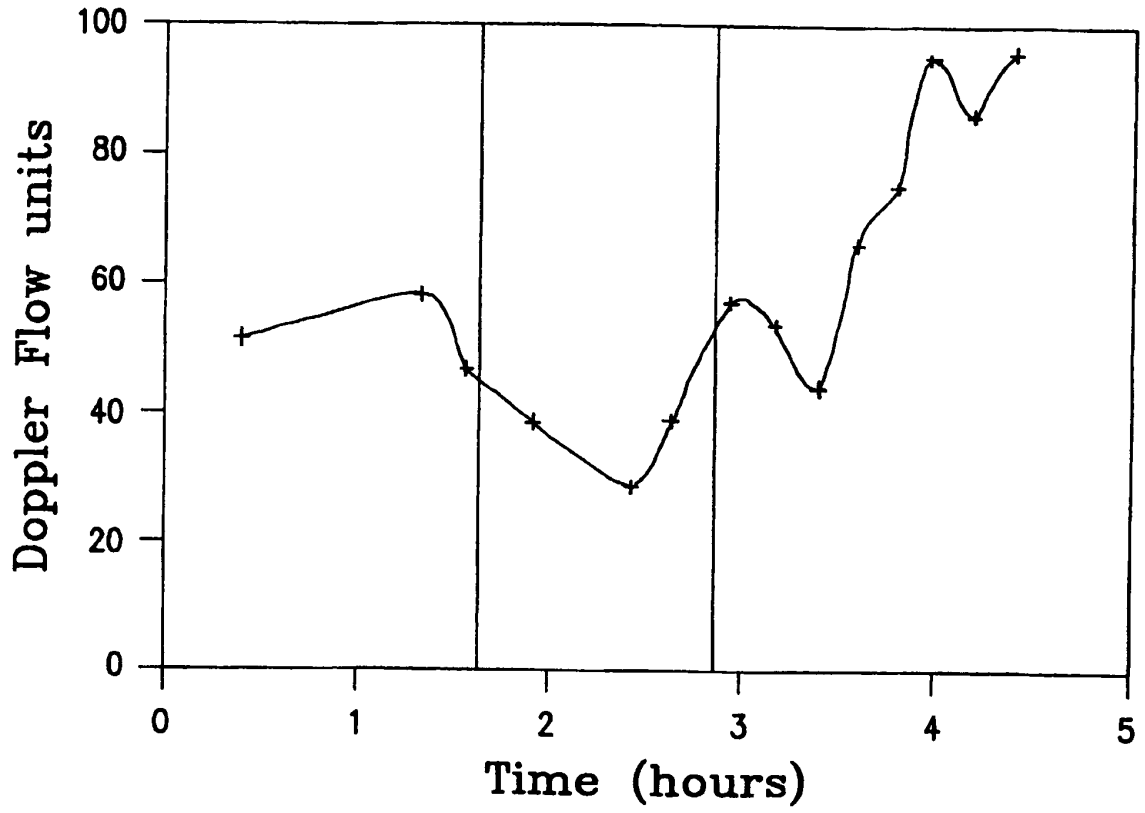


FIG. 2

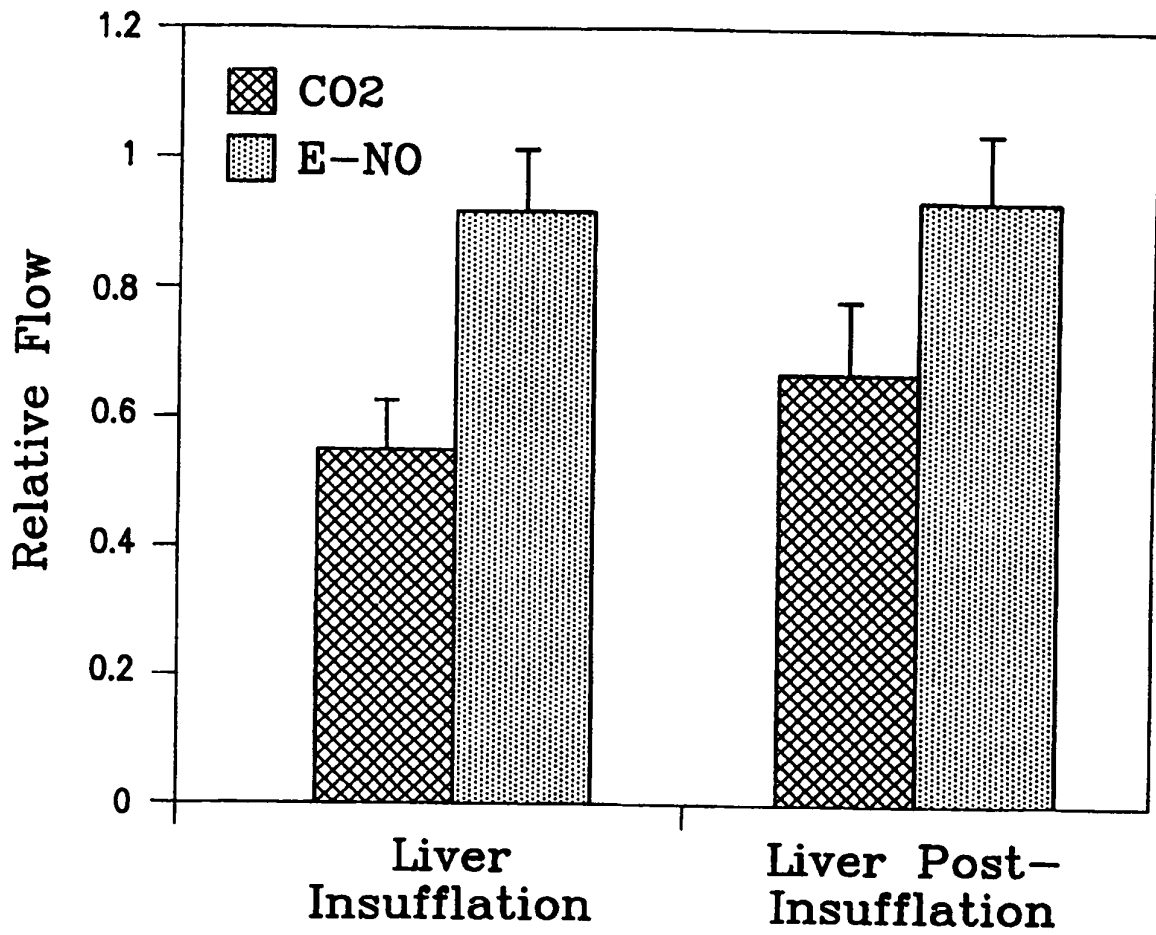


FIG. 3

**REFERENCES CITED IN THE DESCRIPTION**

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专利名称(译)	使用血流减少防止剂与吹入气体一起使用		
公开(公告)号	<a href="#">EP1420851B1</a>	公开(公告)日	2011-12-07
申请号	EP2002746630	申请日	2002-07-12
[标]申请(专利权)人(译)	杜克大学		
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当前申请(专利权)人(译)	杜克大学		
[标]发明人	STAMLER JONATHAN S		
发明人	STAMLER, JONATHAN, S.		
IPC分类号	A61K31/21 A61M31/00 A61P9/10 A61K33/00 A61B19/00 A61B17/34 A61K9/12 A61K45/00		
CPC分类号	A61B17/34 A61B17/3474 A61K31/04 A61K31/21 A61K33/00 A61M31/00 A61M2202/02 A61M2210/1017 A61P1/00 A61K2300/00		
优先权	09/919931 2001-08-02 US		
其他公开文献	EP1420851A1 EP1420851A4		
外部链接	<a href="#">Espacenet</a>		

摘要(译)

血流减少防止剂用于消除或减少由吹入气体引起的腹部器官中氧气输送的减少。 优选地，将气体基本上由注入气体和防止血流减少剂输送到腹腔中。 非常优选地，使用基本上由二氧化碳作为吹入气体并且由亚硝酸乙酯作为向腹部器官的血流减少防止剂的气体组成的气体。

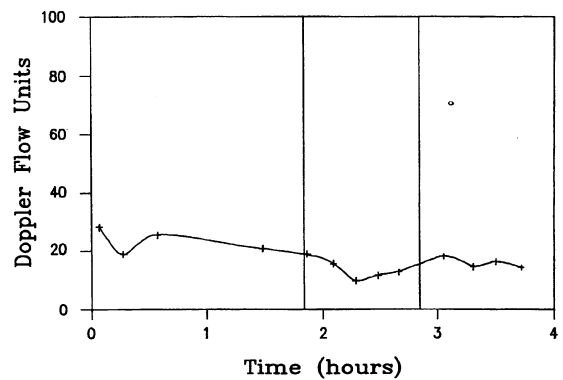


FIG. 1