DISCUSSION

The number of patients with pulmonary hypertension had increased because of increased awareness, better diagnostic techniques and longer survival with the development of more effective treatment options.[91]Thus, more patients with pulmonary hypertension were likely to require elective or emergency surgery. Notably, surgeries in pulmonary hypertension patients carried higher morbidity and mortality. [91]

Pulmonary hypertension leading to right-heart failure is an important cause of morbidity and mortality in cardiac patients. Successful perioperative management of these patients involved avoidance of factors that could precipitate pulmonary hypertensive crisis as well as use of drugs that could lower pulmonary vascular tone. Traditional therapeutic strategy for pulmonary artery hypertension had consisted of intravenous vasodilators (nitroglycerin, sodium nitroprusside, prostaglandins and phosphodiesterase inhibitors). [92]

These pharmacologic agents had been used to limit the increase in pulmonary vascular resistance and pulmonary hypertension after surgery. These parenteral vasodilators lack pulmonary vasculature selectivity and systemic arterial hypotension was induced, limiting their use. Therefore, administration of these drugs by the inhalation route had become more popular because of pulmonary vascular selectivity and the theoretical avoidance of systemic arterial hypotension. [93]

The most commonly used therapy by the inhalation route was nitric oxide, but this was expensive, required specialized equipment and there was concern regarding its toxicity. [92]

The search for inhaled selective pulmonary vasodilators was an active area of research, particularly in Europe and Australia, before the widespread publicity and testing of inhaled nitric oxide in the early 1990s. However, researches on this subject appear to have declined inversely with the growing acceptance and use of inhaled nitric oxide.

Until FDA approval had been granted, inhaled nitric oxide had been supplied free of charge in the United States on an investigational-drug basis. However, after FDA approval, the cost of treatment with inhaled nitric oxide became very expensive. This prompted a search for alternative agents to inhaled nitric oxide. The purpose of this research was to review the published experience concerning alternative inhaled vasodilators.

Inhaled nitric oxide donor drugs might be an effective, readily available, inexpensive alternative or bridge to inhaled nitric oxide therapy, especially in areas where inhaled nitric oxide and extracorporeal membrane oxygenation were inaccessible.

Nitroglycerin, a nitric oxide donor drug, had been found to be effective via the inhaled route in reducing pulmonary hypertension in adult cardiac patients undergoing mitral valve surgery. Milrinone, when given via the nebulized route, had also been shown to result in a greater chance of successful weaning from cardiopulmonary bypass in high risk cardiac patients. Nitroglycerin had been used via the inhaled route in children with pulmonary hypertension but the data were very limited. From the above facts, it was hypothesized that inhaled milrinone and nitroglycerin would significantly reduce pulmonary artery pressure and pulmonary vascular resistance. [92]

In the present study, the aim of this work was to study the effects of inhaled milrinone versus inhaled nitroglycerin on pulmonary and systemic haemodynamics in children with pulmonary hypertension associated with acyanotic congenital heart disease undergoing cardiac catheterization.

This prospective randomized study was carried out in the pediatric cardiac catheterization centre at El-Shatby Pediatric Alexandria university hospital after approval of the medical ethical committee. Each parent received verbal and plain language written description of the research protocol and informed consent were taken from the parents.

Thirty six children below age 4 years suffering from acyanotic congenital heart disease and left to right shunt with pulmonary hypertension (defined by mean pulmonary arterial pressure exceeding 25 mmHg at rest or 30 mmHg during exercise) who required pediatric cardiac catheterization were enrolled prospectively to participate in this study.

Patients were randomized into two equal groups (18 patients each) using closed envelope method.

- **Group I:** Patients received inhaled nitroglycerin in oxygen.
- **Group II:** Patients received inhaled milrinone in oxygen.

Heart rate changes

In the present study, there was; no statistically significant difference between values at 15 minutes after drug administration (After 15) and baseline values (5 minutes after induction) within the groups. Also, there was no significant difference between group I and group II as regards heart rate measurements taken pre-induction(Pre-I), 5 minutes after induction(After 5) and 15 minutes after drug administration(After 15).

In agreement with results of the present study**, Singh et al** [92] carried out a randomized clinical trial to compare the acute effects of inhaled milrinone and inhaled nitroglycerin in a dose of 50µg/kg on pulmonary and systemic hemodynamics in children with acyanotic congenital heart disease (left-to-right shunt) and pulmonary hypertension. They found that inhaled milrinone and nitroglycerin had no significant changes in heart rate. This was explained by more selective effect of these drugs on pulmonary vasculature when given through inhaled route. [92]

Also, **Mansour** [93] in a randomized double blinded study, compared the role of nitroglycerine in a dose of 2.5µg/kg/min, milrinone in a dose of 1mg/ml and iloprost in a dose of 10µg/ml as pulmonary vasodilators administered through the inhalation route in reducing pulmonary hypertension and facilitating weaning from cardiopulmonary bypass in cardiac surgical patients. He observed that there was stable heart rate throughout the operative time explained by pulmonary vasodilators selectivity of these drugs when administered by the inhalation route. [93]

Moreover, **Mandal et al** [94] conducted a study to compare the acute hemodynamic effects of inhaled nitroglycerin in a dose of 2.5µg/kg/min, intravenous nitroglycerin in a dose of 2.5µg/kg/min and their combination with intravenous dobutamine in patients with secondary pulmonary hypertension. They revealed that inhaled nitroglycerin produced

selective pulmonary vasodilator without significant changes in heart rate. On contrary they reported that intravenous nitroglycerin increase heart rate. (94)

Also, **Goyal et al** (95) investigated the acute effects of inhaled nitroglycerin in a dose of 2.5µg/kg/min on pulmonary and systemic haemodynamics in children with pulmonary hypertension associated with congenital heart disease. They showed that nitroglycerin inhalation significantly decreased systolic, diastolic and mean pulmonary artery pressure as well as pulmonary vascular resistance and pulmonary vascular resistance index without affecting heart rate in children with severe pulmonary hypertension secondary to congenital heart disease.(95)

Moreover, **Denault et al** (96) conducted out a pilot randomized controlled trial of inhaled milrinone in a dose of 50µg/kg in high risk cardiac surgical patients. They reported that the administration of inhaled milrinone was not associated with any significant heart rate changes. (96)

Similarly**, Hongmei et al** (97) carried out a study to compare inhaled and intravenous milrinone in a dose of 50µg/kg in patients with pulmonary hypertension undergoing mitral valve replacement surgery. They reported that heart rate did not change with inhaled milrinone explained by selective pulmonary vasorelaxation.(97)

In contrast with results of the present study, **Hegazy et al** (98) carried a study to compare hemodynamic effects of inhaled milrinone in a dose of 50µg/kg and inhaled prostacyclin after adult cardiac surgery. They revealed that milrinone treated patients tended to have a higher heart rate and lower mean systemic blood pressure. It was unclear if the lower mean systemic blood pressure in the milrinone group induced a reflex tachycardia or the higher heart rate was a result of chronotropic effect of milrinone or due to higher dose used. (98)

In the present study, steady heart rate could be attributed to pulmonary vascular selectivity for these drugs administered by inhalation.

Systemic arterial blood pressure changes

In the present study, there was; no statistically significant difference between values at 15 minutes after drug administration (After 15) and baseline values (5 minutes after induction) within the groups. Also, there was no significant difference between group I and group II as regards systolic, diastolic and mean systemic arterial blood pressure measurements taken pre-induction(Pre-I) , 5 minutes after induction (After 5) and 15 minutes after drug administration (After 15).

In agreement with results of the present study**, Mansour** (93) in randomized double blinded study, compared the role of nitroglycerine in a dose of 2.5µg/kg/min, milrinone in a dose of 1mg/ml and iloprost in a dose of 10µg/ml as pulmonary vasodilators administered through the inhalation route in reducing pulmonary hypertension and facilitating weaning from cardiopulmonary bypass in cardiac surgical patients. He found that these drugs administered by inhalation produce maintenance of the systemic vascular resistance and mean systemic blood pressure throughout the operative time. He explained that by pulmonary vasodilators selectivity of these drugs when administered by the inhalation route. (93)

Also, **Singh et al** [92] carried out a randomized clinical trial to compare the acute effects of inhaled milrinone and inhaled nitroglycerin in a dose of 50µg/kg on pulmonary and systemic hemodynamics in children with acyanotic congenital heart disease (left-to-right shunt) and pulmonary hypertension. They reported that inhaled milrinone and nitroglycerin had no significant changes in heart rate or systemic pressures. This was explained by the more selective effect of these drugs on pulmonary vasculature when given through the inhaled route. [92]

Moreover, **Yurtseven et al** [99] conducted a study to compare the acute hemodynamic effects of nitroglycerin inhalation in a dose of 20µg/kg and inhaled iloprost in a dose of 2.5µg/kg in patients with pulmonary hypertension undergoing mitral valve replacement surgery. They reported that inhaled nitroglycerine was pulmonary vascular selectivity, evidenced by stable mean systemic blood pressure. [99]

Also, **Kang et al** [100] investigated effect of nebulized nitroglycerin in a dose of 20µg/kg on children with ventricular septal defect and pulmonary hypertension. They showed that inhaled nitroglycerin could decrease pulmonary artery pressure but did not significantly decrease the systemic blood pressure in children with ventricular septal defect with pulmonary hypertension. This was explained by producing desired local vasodilation by liberating nitric oxide. [100]

Moreover, **Hentschel et al** [101] studied the effects of inhaled milrinone in a dose of 1mg/ml and intravenous milrinone in a dose of 1µg/kg/min on pulmonary and systemic hemodynamics in a rat model of congestive heart failure. They observed that inhalation of milrinone reduced mean pulmonary artery pressure effectively without exerting systemic hemodynamic effects. This was explained by the action of inhaled milrinone was predominantly confined to the pulmonary vasculature. But intravenous milrinone exert a systemic hemodynamics effects. [101]

Also, **Sablotzki et al** [82] conducted out a pilot study to test the hypothesis that inhaled milrinone in a dose of 2mg may cause selective pulmonary vasodilation on heart transplant candidates. They revealed that patients with pulmonary hypertension developed a significant decrease of mean pulmonary artery pressure which lasted for only a short period and there were no effects on systemic hemodynamics. [82]

In contrast with results of the present study, **Bando et al** [102] studied effects of inhalation of nitroglycerin in a dose of 2.5µg/kg/min on hypoxic pulmonary vasoconstriction in dogs. They reported that nitroglycerin inhalation decreased mean systemic blood pressure, mean pulmonary artery pressure and pulmonary vascular resistance but did not affect cardiac output. This could be attributed to different hemodynamics in dogs. [102]

Also, **Hegazy et al** [98] conducted out a study to compare hemodynamic effects of inhaled milrinone in a dose of 50µg/kg and inhaled prostacyclin after adult cardiac surgery. They observed that inhaled milrinone induced a statistically significant decrease pulmonary vascular resistance and mean pulmonary artery pressure without significant decrease in mean systemic blood pressure and systemic vascular resistance. This could be attributed to higher dose used. [98]

In the present study, systemic arterial blood pressure stability could be attributed, to selective pulmonary vasodilator effect of these drugs without spillover of the drug in the systemic circulation.

Pulmonary blood pressure changes

In the present study, there was a significant decrease between values at 15 minutes after drug administration (After 15) and baseline values (5 minutes after induction) within the groups. But there was no significant difference between group I and group II as regards systolic, diastolic and mean pulmonary blood pressure measurements taken 15 minutes after drug administration (After 15) and 5 minutes after induction (After 5).

In agreement with results of the present study, **Singh et al** [92] in a randomized clinical trial, compared the acute effects of inhaled milrinone and inhaled nitroglycerin in a dose of 50µg/kg on pulmonary and systemic hemodynamics in children with acyanotic congenital heart disease (left-to-right shunt) and pulmonary hypertension. They found that both inhaled milrinone and inhaled nitroglycerin led to significant decrease in systolic, diastolic and mean pulmonary artery pressures but no difference between the two groups. This was explained by more selective effect of these drugs on pulmonary vasculature when given through the inhaled route. [92]

Also, **Haraldson et al** [103] studied additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in a dose of 3mg in postcardiac surgical patients with pulmonary hypertension **and Yurtseven et al** [99] carried out a study to compare the acute hemodynamic effects of nitroglycerin inhalation in a dose of 20µg/kg and iloprost in a dose of 2.5 µg/kg in patients with pulmonary hypertension undergoing mitral valve replacement surgery. Both authors reported that inhaled milrinone and nitroglycerin had similar selective reductions of mean pulmonary blood pressure, pulmonary vascular resistance and intrapulmonary shunt. This was explained by pulmonary vascular selectivity of these drugs.[99,103]

Moreover, **Goyal et al** [95] investigated the acute effects of inhaled nitroglycerin in dose of 2.5µg/kg/min on pulmonary and systemic haemodynamics in children with pulmonary hypertension associated with congenital heart disease. They concluded that nitroglycerin inhalation significantly decreased systolic, diastolic and mean pulmonary artery pressures in children with severe pulmonary hypertension secondary to congenital heart disease. [95]

Similarly, **Omar et al** [104] carried out a study to investigate the effects of nitroglycerin inhalation in a dose of 20µg/kg in pulmonary hypertension resulting from congenital cardiac disease. They reported decrease in systolic pulmonary artery pressure and mean pulmonary artery pressure as a result of nitroglycerin administration by inhalational route. [104]

Also, **Hegazy et al** [98] conducted out a study to compare hemodynamic effects of inhaled milrinone in a dose of 50µg/kg and inhaled prostacyclin after adult cardiac surgery. They showed that inhaled milrinone induced a statistically significant decrease mean pulmonary artery pressure. This was explained by pulmonary vasodilator selectivity. [98]

Furthermore**, Lamarche et al** [105] studied a preliminary experience in patients had received inhaled milrinone in a dose of 50µg/kg; the major findings in their study were, in high-risk patients with similar preoperative and operative characteristics. They observed that administration of a single bolus of inhaled milrinone before initiation of cardiopulmonary bypass was associated with lower mean pulmonary artery pressure. This was explained by preservation of pulmonary arterial endothelial function and increased cyclic adenosine monophosphate content in pulmonary artery cells favoring vasodilatation. [105]

In contrast with results of the present study, **Mansour** [93] carried out a randomized double blinded study to compare the role of nitroglycerine in a dose of 2.5µg/kg/min, milrinone in a dose of 1mg/ml and iloprost in a dose of 10µg/ml as pulmonary vasodilators administered through the inhalation route in reducing pulmonary hypertension and facilitating weaning from cardiopulmonary bypass in cardiac surgical patients. He found that mean pulmonary blood pressure and pulmonary vascular resistance decreased significantly in both groups when compared with the baseline values. This was explained by pulmonary vasodilators selectivity of these drugs when administered by the inhalation route. But this decrease in mean pulmonary blood pressure and pulmonary vascular resistance was significantly greater in the milrinone group compared with nitroglycerine group. This could be attributed to higher dose of milrinone used. [93]

In the present study, the decrease in systolic, diastolic and mean pulmonary artery pressures could be attributed to pulmonary vascular selectivity for these drugs administered by inhalation. Nitroglycerine is metabolized to nitric oxide, which cause vasodilatation by activating the guanylate cyclase enzyme and increasing cyclic guanosine monophosphate in vascular smooth muscles and induce selective pulmonary vasodilatation when administered by the inhalation route. Milrinone is a phosphodiesterase-III inhibitor that increase the intracellular levels of cyclic adenosine monophosphate exerting a positive myocardial inotropic effect and pulmonary vasodilatation.

Oxygen saturation and partial pressure changes

In the present study, there was a significant increase in both parameters between values at 15 minutes after drug administration (After 15) and baseline values (5 minutes after induction) within the groups. But there was no significant difference between group I and group II as regards oxygen saturation and partial pressure measurements from the superior vena cava, pulmonary artery and femoral artery taken 15 minutes after drug administration (After 15) and 5 minutes after induction (After5).

In agreement with results of the present study**, Goyal et al** [95] investigated the acute effects of inhaled nitroglycerin in a dose of 2.5µg/kg/min on pulmonary and systemic haemodynamics in children with pulmonary hypertension associated with congenital heart disease. They concluded that oxygen saturation and partial pressure measurements after nitroglycerin inhalation were significantly higher than baseline values. This was explained by advantage of the inhalational route of administration, in which vasodilator drug is preferentially distributed to well ventilated lung areas, effecting a redistribution of blood flow from non-ventilated regions to these areas, thereby reducing the ventilation/perfusion mismatch and intrapulmonary shunt fraction. [95]

Also, **Nurgul et al** [106] investigated the hemodynamic effects of nitroglycerin inhalation in a dose of 2.5µg/kg/min on patients with pulmonary hypertension undergoing

mitral valve replacement surgery. They showed that inhaled nitroglycerin increase oxygen saturation and oxygen partial pressure. This was explained by inhaled nitroglycerin produce vasodilatation of pulmonary vasculature adjacent to well-ventilated alveoli, increases blood flow to these areas and preferentially shunts blood away from poorly ventilated regions; thus, it match ventilation/perfusion and reduce intrapulmonary shunt. This results in improved oxygenation and reduced pulmonary vascular resistance and right ventricular afterload. (106)

Moreover, **Hongmei et al** (97) conducted out a study to compare inhaled and intravenous milrinone in a dose of 50µg/kg in patients with pulmonary hypertension undergoing mitral valve replacement surgery. They revealed that after milrinone inhalation increase in oxygen saturation and partial pressure. This was explained by vasodilation of pulmonary vasculature adjacent to well ventilated alveoli, increase blood flow to these areas and preferentially shunts blood away from poorly ventilated regions thus it match ventilation/perfusion ratio and reduce intrapulmonary shunt. This results in improved oxygenation. On contrary, they reported that intravenous milrinone produce pulmonary vasodilation in both ventilated and non-ventilated alveoli leading to increase intrapulmonary shunt and hence hypoxemia. (97)

Also, **Hentschel et al** (101) studied the effects of inhaled milrinone in a dose of 1mg/ml and intravenous milrinone in a dose of 1µg/kg/min on pulmonary and systemic hemodynamics in a rat model of congestive heart failure. They found that there was increase in oxygen saturation and partial pressure in the inhaled milrinone group but not in the intravenous group further suggests a beneficial potential for inhaled milrinone. (101)

In contrast with results of the present study, **Mansour** (93) in randomized double blinded study, compared the role of nitroglycerine in a dose of 2.5µg/kg/min, milrinone in a dose of 1mg/ml and iloprost in a dose of 10µg/ml as pulmonary vasodilators administered through the inhalation route in reducing pulmonary hypertension and facilitating weaning from cardiopulmonary bypass in cardiac surgical patients. He found that milrinone and nitroglycerin induced a significant increase in oxygen saturation and partial pressure in comparison with the baseline values. But oxygen saturation and partial pressure were significantly greater in the milrinone group compared with nitroglycerine group. This could be attributed to higher dose of milrinone used. (93)

In the present study, the increase oxygen partial pressure and oxygen saturation could be attributed that inhaled nitroglycerin induced a significant increase in oxygen saturation and partial pressure due to selective pulmonary vasodilator without inhibition of hypoxic pulmonary vasoconstriction, indicating the advantage of the inhalational route of administration, in which vasodilator drug is preferentially distributed to well-ventilated lung areas, effecting a redistribution of blood flow from non-ventilated regions to these areas, thereby reducing the ventilation/perfusion mismatch and intrapulmonary shunt fraction. Also increase in oxygen saturation and partial pressure with inhaled milrinone could be attributed to vasodilation of pulmonary vasculature adjacent to well ventilated alveoli, increase blood flow to these areas and preferentially shunts blood away from poorly ventilated regions thus it match ventilation/perfusion ratio and reduce intrapulmonary shunt.

Pulmonary vascular resistance index changes

In the present study, there was a significant decrease between values at 15 minutes after drug administration (After 15) and baseline values (5 minutes after induction) within the groups. But there was no significant difference between group I and group II as regards pulmonary vascular resistance index measurements taken 15 minutes after drug administration (After 15) and 5 minutes after induction (After 5).

In agreement with results of the present study, **Singh et al** [92] in a randomized clinical trial, compared the acute effects of inhaled milrinone and inhaled nitroglycerin in a dose of 50µg/kg on pulmonary and systemic hemodynamics in children with acyanotic congenital heart disease (left-to-right shunt) and pulmonary artery hypertension. They found that both inhaled milrinone and inhaled nitroglycerin led to significant decrease in systolic, diastolic and mean pulmonary artery pressures. These drugs also cause a decrease in pulmonary vascular resistance index, highlighting a more selective effect on pulmonary vasculature when given through the inhaled route but no difference between two groups was reported. [92]

Also, **Haraldson et al** [103] studied additive pulmonary vasodilatory effects of inhaled prostacyclin and inhaled milrinone in a dose of 3mg in postcardiac surgical patients with pulmonary hypertension **and Yurtseven et al** [99] conducted out a study to compare the acute hemodynamic effects of nitroglycerin inhalation in a dose of 20µg/kg and iloprost in a dose of 2.5 µg/kg in patients with pulmonary hypertension undergoing mitral valve replacement surgery. Both authors found that inhaled milrinone and nitroglycerin had similar selective reductions of mean pulmonary blood pressure, pulmonary vascular resistance, pulmonary vascular resistance index and intrapulmonary shunt. This was explained by pulmonary vascular selectivity. [99,103]

Moreover**, Mandal et al** [94] conducted out a study to compare the acute hemodynamic effects of inhaled nitroglycerin in a dose of 2.5µg/kg/min, intravenous nitroglycerin in a dose of 2.5µg/kg/min and their combination with intravenous dobutamine in patients with secondary pulmonary hypertension. They showed that inhaled nitroglycerin produced significant decrease in mean pulmonary artery pressure, pulmonary vascular resistance and pulmonary vascular resistance index. This was explained by selective pulmonary vasodilator. On contrary they reported that intravenous nitroglycerin decrease mean systemic blood pressure, mean pulmonary blood pressure, pulmonary vascular resistance index and systemic vascular resistance index. [94]

Also, **Goyal et al** [95] investigated the acute effects of inhaled nitroglycerin in a dose of 2.5µg/kg/min on pulmonary and systemic haemodynamics in children with pulmonary hypertension associated with congenital heart disease. They revealed that nitroglycerin inhalation significantly decreased systolic, diastolic and mean pulmonary artery pressures as well as pulmonary vascular resistance and pulmonary vascular resistance index in children with severe pulmonary hypertension secondary to congenital heart disease. [95]

Moreover, **Denault et al** [96] conducted out a pilot randomized controlled trial of inhaled milrinone in a dose of 50µg/kg in high risk cardiac surgical patients. They observed that the administration of inhaled milrinone decrease pulmonary vascular resistance and pulmonary vascular resistance index. [96]

Also, **Sablotzki et al** [82] carried out a pilot study to test the hypothesis that inhaled milrinone in a dose of 2mg may cause selective pulmonary vasodilation on heart transplant candidates. They found that patients with pulmonary hypertension developed a significant decrease of mean pulmonary artery pressure, pulmonary vascular resistance and pulmonary vascular resistance index. [82]

In contrast with result of the present study, **Mansour** [93] in a randomized double blinded study, compared the role of nitroglycerine in a dose of 2.5 µg/kg/min, milrinone in a dose of 1mg/ml and iloprost in a dose of 10µg/ml as pulmonary vasodilators administered through the inhalation route in reducing pulmonary hypertension and facilitating weaning from cardiopulmonary bypass in cardiac surgical patients. He found that mean pulmonary artery pressure, pulmonary vascular resistance and pulmonary vascular resistance index decreased significantly in both groups when compared with the baseline values. This was explained by pulmonary vasodilators selectivity of these drugs when administered by the inhalation route. This decrease in mean pulmonary artery pressure, pulmonary vascular resistance and pulmonary vascular resistance index were significantly greater in the milrinone group compared with nitroglycerine group. This could be attributed to higher dose of milrinone used. [93]

In present study, the decrease in pulmonary vascular resistance index could be attributed to that nitroglycerine is metabolized to nitric oxide, which causes vasodilatation by activating the guanylate cyclase enzyme and increasing cyclic guanosine monophosphate in vascular smooth muscles and induce selective pulmonary vasodilatation when administered by the inhalation route. Milrinone is a phosphodiesterase-III inhibitor that increase the intracellular levels of cyclic adenosine monophosphate, exerting a positive myocardial inotropic effect and pulmonary vasodilatation.

Systemic vascular resistance index changes

In the present study, there was a significant decrease between values at 15 minutes after drug administration (After 15) and baseline values (5 minutes after induction) within the groups. But there was no significant difference between group I and group II as regards systemic vascular resistance index measurements taken 15 minutes after drug administration (After 15) and 5 minutes after induction (After 5).

In agreement with results of the present study, **Singh et al** [92] conducted a randomized clinical trial to compare the acute effects of inhaled milrinone and inhaled nitroglycerin in a dose of 50µg/kg on pulmonary and systemic hemodynamics in children with acyanotic congenital heart disease (left-to-right shunt) and pulmonary artery hypertension. They observed that these drugs cause a decrease in pulmonary vascular resistance index and systemic vascular resistance index, but the effect on systemic vascular resistance index was small compared with the effect on pulmonary vascular resistance index, highlighting a more selective effect on pulmonary vasculature when given through the inhaled route but no difference between the two groups was reported. [92]

Also, **Denault et al** [96] conducted out a pilot randomized controlled trial of inhaled milrinone in a dose of 50µg/kg in high risk cardiac surgical patients. They showed that the administration of inhaled milrinone decrease systemic vascular resistance and systemic vascular resistance index and no patient presented with systemic hypotension. [96]

Moreover, **Hegazy et al** [98] carried out a study to compare hemodynamic effects of inhaled milrinone in a dose of 50µg/kg and inhaled prostacyclin after adult cardiac surgery. They reported that inhaled milrinone induced a statistically significant decrease in mean pulmonary artery pressure and pulmonary vascular resistance without significant decrease in mean systemic blood pressure, systemic vascular resistance and systemic vascular resistance index. This was explained by pulmonary vasodilator selectivity. [98]

In contrast with result of the present study**, Mansour** [93] in a randomized double blinded study, compared the role of nitroglycerine in a dose of 2.5µg/kg/min, milrinone in a dose of 1mg/ml, and iloprost in a dose of 10 µg/ml as pulmonary vasodilators administered through the inhalation route in reducing pulmonary hypertension and facilitating weaning from cardiopulmonary bypass in cardiac surgical patients. He found that these drugs administered by inhalation, produce stable systemic vascular resistance, systemic vascular resistance index and mean systemic blood pressure throughout the operative time. This was explained by pulmonary vasodilators selectivity of these drugs when administered by the inhalation route. [93]

Also**, Gong et al** [80] investigated effect of nebulized nitroglycerin in a dose of 20µg/kg on dogs with experimental pulmonary hypertension. They showed that nebulized nitroglycerin decrease systolic, diastolic and mean pulmonary artery pressures a without affecting systolic, diastolic and mean systemic blood pressures and systemic vascular resistance index. This was explained by pulmonary vascular selectivity. [80]

Moreover, **Nurgul et al** [106] conducted out a study to investigate the hemodynamic effects of nitroglycerin inhalation in a dose of 2.5µg/kg/min on patients with pulmonary hypertension undergoing mitral valve replacement surgery. They concluded that inhaled nitroglycerin reduce mean pulmonary artery pressure and pulmonary vascular resistance without affecting systemic vascular resistance and systemic vascular resistance index. [106]

Also, **Hongmei et al** [97] compared inhaled and intravenous milrinone in a dose of 50µg/kg in patients with pulmonary hypertension undergoing mitral valve replacement surgery. They revealed that, after milrinone inhalation selective pulmonary vasorelaxation was achieved with mean pulmonary artery pressure and pulmonary vascular resistance values decrease significantly while mean systemic blood pressure, systemic vascular resistance and systemic vascular resistance index were not affected. On contrary they reported that intravenous milrinone decrease mean systemic arterial blood pressure, mean pulmonary blood pressure, pulmonary vascular resistance index and systemic vascular resistance index. [97]

Also, **Hentschel et al** [101] studied the effects of inhaled milrinone in a dose of 1mg/ml and intravenous milrinone in a dose of 1µg/kg/min on pulmonary and systemic hemodynamics in a rat model of congestive heart failure. They found that inhalation of milrinone reduced pulmonary artery pressure effectively without exerting systemic hemodynamic effects. This was explained by the action of inhaled milrinone was predominantly confined to the pulmonary vasculature. On contrary, they reported that intravenous milrinone reduced pulmonary arterial blood pressure, systemic arterial blood pressure, pulmonary vascular resistance index and systemic vascular resistance index. [101]

In the present study, the decrease in systemic vascular resistance index could be attributed that, these drugs cause a decrease in pulmonary vascular resistance index and systemic vascular resistance index but the effect on systemic vascular resistance index was small compared with the effect on pulmonary vascular resistance index, highlighting a more selective effect on pulmonary vasculature when given through the inhaled route. The maintenance of systemic pressures even in the presence of a fall in systemic vascular resistance index could be attributed to improve pulmonary blood flow and cardiac output.

Changes in pulmonary to systemic blood flow ratio

In the present study, there was a significant increase between values at 15 minutes after drug administration (After 15) and baseline values (5 minutes after induction) within the groups. But there was no significant difference between group I and group II as regards pulmonary to systemic blood flow ratio measurements taken 15 minutes after drug administration (After 15) and 5 minutes after induction (After 5).

In agreement with results of the present study, **Singh et al** [92] carried out a randomized clinical trial to compare the acute effects of inhaled milrinone and inhaled nitroglycerin in a dose of 50µg/kg on pulmonary and systemic hemodynamics in children with acyanotic congenital heart disease (left to right shunt) and pulmonary hypertension. They found that pulmonary to systemic blood flow ratio (Qp/Qs) increased significantly with both drugs but no difference between the two groups was reported. [92]

Also, **Goyal et al** [95] investigated the acute effects of inhaled nitroglycerin in a dose of 2.5µg/kg/min on pulmonary and systemic haemodynamics in children with pulmonary hypertension associated with congenital heart disease. They reported that nitroglycerin inhalation significantly increase pulmonary to systemic blood flow ratio (Qp/Qs). [95]

Also, **Kang et al** [100] investigated effect of nebulized nitroglycerin in a dose of 20µg/kg on children with ventricular septal defect and pulmonary hypertension. They showed that inhaled nitroglycerin could increase pulmonary to systemic blood flow ratio (Qp/Qs) more than 2.5 in children with ventricular septal defect with pulmonary hypertension. [100]

In the present study, increase pulmonary to systemic blood flow ratio (Qp/Qs) might be due to the decrease in pulmonary vascular resistance index was more than decrease in systemic vascular resistance index leading to high pulmonary blood flow. [92,100]

So, Based on the evidence to date, it would appear that other selective pulmonary vasodilators might be as effective as inhaled nitric oxide with less potential for toxicity, significantly lower costs and greater ease of administration.

The study demonstrated that both inhaled milrinone and inhaled nitroglycerin were similar in efficacy and did not offer any major advantage over each other.

Nitroglycerin was, however, cheaper and a more cost effective drug compared with milrinone. These drugs did not require any specialized equipment as was needed for inhaled nitric oxide, which also had the additional risk of toxicity (methemoglobinemia, pulmonary cytotoxicity).

One hundred percent oxygen is one of the most potent pulmonary vasodilators, but such high inspired oxygen concentrations for prolonged periods could lead to oxygen toxicity. Therefore, these drugs given via the nebulized route would be beneficial adjuvants for lowering the required oxygen concentrations during perioperative management of pulmonary artery hypertensive episodes.

Thus it could be used as an alternative mode of therapy in reducing pulmonary hypertension in children with congenital heart disease, mainly in clinical situations where acute reduction of pulmonary artery pressure was needed and at places where facilities for inhaled nitric oxide administration were not available.

SUMMARY

Incidence of congenital heart disease (CHD) is about 0.8% and most of these congenital heart disease children (80%) survive to adulthood in developed countries due to early diagnosis and intervention along with improved surgical and anaesthetic techniques. But the situation was different in most of the third world countries, where 90% of these children receive suboptimal or no care. The number of patients with pulmonary hypertension had increased because of increased awareness, better diagnostic techniques and longer survival with the development of more effective treatment options. Thus, more patients with pulmonary hypertension were likely to require elective or emergency surgery. Notably, surgeries in pulmonary hypertension patients carried higher morbidity and mortality.

Pulmonary hypertension leading to right heart failure is an important cause of morbidity and mortality in cardiac patients. Successful perioperative management of these patients involved avoidance of factors that could precipitate pulmonary hypertensive crisis as well as use of drugs that could lower pulmonary vascular tone. Traditional therapeutic strategy for pulmonary artery hypertension had consisted of intravenous vasodilators (nitroglycerin, sodium nitroprusside, prostaglandins and phosphodiesterase inhibitors).

These pharmacologic agents had been used to limit the increase in pulmonary vascular resistance and pulmonary hypertension after surgery. These parenteral vasodilators lack pulmonary vasculature selectivity and systemic arterial hypotension was induced, limiting their use. Therefore, administration of these drugs by the inhalation route had become more popular because of pulmonary vascular selectivity and the theoretical avoidance of systemic arterial hypotension. The most commonly used therapy by the inhalation route was nitric oxide, but this was expensive, require specialized equipment and there was concern regarding its toxicity.

The aim of this work was to study the effects of inhaled milrinone versus inhaled nitroglycerin on pulmonary and systemic haemodynamics in children with pulmonary hypertension associated with acyanotic congenital heart disease undergoing cardiac catheterization.

This prospective randomized study was carried out in the pediatric cardiac catheterization centre at El-Shatby Pediatric Alexandria university hospital after approval of the medical ethical committee. Each parent received verbal and plain language written description of the research protocol and informed consent were taken from the parents. Thirty six children below age 4 years suffering from acyanotic congenital heart disease and left to right shunt with pulmonary hypertension [defined by mean pulmonary arterial pressure exceeds 25 mmHg at rest or 30 mmHg during exercise] who required pediatric cardiac catheterization were enrolled prospectively to participate in this study. Patients were randomly categorized into two equal groups (18 patients each), patients received either inhaled nitroglycerin or inhaled milrinone. Patients with coagulopathy, cyanotic heart disease, primary pulmonary hypertension, Eisenmenger syndrome, Trisomy 21, those receiving sedative drugs or on inotropic drugs and also those already receiving vasodilator treatment were excluded from study.

Standard anaesthetic technique was used in all the patients. After application of EMLA cream, intravenous line was inserted. Monitors were attached which include ECG leads, pulse oximeter and noninvasive blood pressure cuff. Injection midazolam (0.01mg/kg) was given intravenous 2 minutes before the induction of anaesthesia. Anaesthesia was induced using propofol 1.5mg/kg and fentanyl 2µg/kg as IV bolus doses. Maintenance of anaesthesia was achieved with infusion of propofol 2mg/kg/h and fentanyl 2 µg/kg/h and respiration was maintained spontaneously with a laryngeal mask of proper size.

After induction and femoral access insertion, baseline heart rate, systolic, diastolic and mean systemic arterial blood pressures were recorded for all patients noninvasively, while pulmonary artery pressures were recorded for all patients invasively. Haemodynamic data were obtained using MAC-LAB 6H, cath lab haemodynamic monitoring system (1996 Marquette Medical Systems Inc., now a part of GE Healthcare worldwide), which provide the electronic mean of all haemodynamic variables. Also samples of blood were collected from the superior vena cava, pulmonary artery (PA) and femoral artery in heparinized syringes to measure saturation and partial pressure of oxygen representing systemic venous, pulmonary arterial and systemic arterial blood respectively. Where pulmonary vascular resistance index (PVRI), systemic vascular resistance index (SVRI) and pulmonary to systemic blood flow ratio (Qp/Qs) were calculated using standard formula based on Fick's principle through computerized program. Data was obtained using MAC-LAB 6H, cath lab haemodynamic monitoring system (1996 Marquette Medical Systems Inc., now a part of GE Healthcare worldwide).

The patients at this point were randomly categorized into two equal groups receiving either nebulized milrinone (group M) or nebulized nitroglycerin (group N) for 10 minutes. Patients received nebulized nitroglycerin or milrinone in the dose of 2.5µg/kg/min for a period of 10 min. (i.e. 25µg/kg of nitroglycerin or milrinone was needed during the 10 min period).

Either nitroglycerin or milrinone 5mg (5ml of 1mg/ml) was dissolved in 20ml normal saline to make a solution of 250µg/ml of drug. The required amount of nitroglycerin was taken with the help of 1ml syringe bearing marks for each 0.1ml, so that 25µg of drug was taken precisely, then 0.1ml of dissolved drug was taken for every 1 kg body weight of patient (i.e. 0.5ml for a 5 kg child) and made up to 3ml with normal saline and nebulized over 10 minutes period using 5-6 litre/min of oxygen. After completion of nebulization, a complete set of hemodynamic and oximetric data were recorded again.

There was no significant difference in demographic data between the two groups. After drug nebulization both groups did not reveal any significant changes in heart rate, systolic, diastolic and mean systemic arterial blood pressures either within group or between the two groups. However, the systolic, diastolic and mean pulmonary pressures decreased significantly in both groups when compared with their baseline values but no difference between the two groups. After drug administration, the PVRI decreased from baseline value to mean of 0.49 ± 0.50 in group N and to a mean of 0.29 ± 0.40 in group M, while SVRI deceased to a mean of 1.67 ± 1.50 in group N and to a mean of 1.43 ± 1.01 in group M also no difference between the two groups. The fall in SVRI was small as compared with fall in PVRI. Oxygen saturation and partial pressure of oxygen increase significantly after drug nebulization when compared with their baseline values while no

difference between the two groups. Pulmonary to systemic blood flow ratio (Qp/Qs) increased significantly to a mean value of 3.60 ± 3.29 in group N and to a mean value of 4.27 ± 3.24 in group M but no difference between the two groups.

It was concluded that nitroglycerin and milrinone inhalation similarly decrease systolic, diastolic and mean pulmonary artery pressures as well as pulmonary vascular resistance index and systemic vascular resistance index while increasing oxygen saturation and oxygen partial pressure in superior vena cava, pulmonary artery and femoral artery and also increase pulmonary to systemic blood flow ratio without affecting systolic, diastolic and mean systemic arterial blood pressures and heart rate in children with pulmonary hypertension secondary to acynotic congenital heart disease.

CONCLUSIONS

From the present study we concluded that nitroglycerin and milrinone inhalation similarly:

1- Produce steady heart rate.
2- Produce stability in systolic, diastolic and mean systemic arterial blood pressures.
3- Decrease in systolic, diastolic and mean pulmonary artery pressures.
4- Decrease in pulmonary vascular resistance index and systemic vascular resistance index.
5- Increase in oxygen saturation and oxygen partial pressure in superior vena cava, pulmonary artery and femoral artery.
6- Increase in pulmonary to systemic blood flow ratio.