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Should Near Systemic Pulmonary Hypertension be a Contraindication for Rheumatic Mitral Stenosis Valve surgery in Egyptian population?

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ORIGINAL STUDY

Should near systemic pulmonary hypertension be a contraindication for rheumatic mitral stenosis valve surgery in Egyptian population?

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Abstract

Background: **Pulmonary hypertension is a well-known risk factor leading to mortality and morbidity in mitral stenosis (MS) patients, in spite of long-term outcome are being comparable regarding severe and mild or moderate pulmonary hypertension but definitely short-term results are worse.**

Objective: **New management protocol to decrease the immediate postoperative differences between patients having MS with near systemic pulmonary hypertension compared to patients with mild or moderate pulmonary hypertension.**

Patients and methods: **Prospective cohort single-centre study was held in National Heart Institute, between 2016 and 2022, on patients undergoing Mitral valve surgery for MS with near systemic hypertension. Inclusion criteria, 18−60 years with isolated MS (± tricuspid valve) and pulmonary hypertension >80 mmHg who will undergo Mitral valve surgery. Previous bosentan or other endothelin receptor antagonist or pulmonary disease that may affect pulmonary artery pressure or a history of pulmonary embolism are excluded from the study. Also patients with other valve disease, redo cases or IHD. Comparison will be done with patients with mild to moderate PH, by assigning patients to 2 groups (PAP> 80 and control PAP< 50), study group will follow the study protocol. Both groups will receive also the standard treatment.**

Results: **No significant difference in preoperative variables apart from NYHA class, Pulmonary artery pressure ($P < 0.001$), operatively cross-clamp time was lower in the study group (32 ± 8.1vs 45 ± 6.8). Postoperatively short-term mortality and morbidity were comparable with the control group.**

Conclusion: **Strict protocol can be a solution for high short-term mortality and morbidity in patients having MS and near systemic pulmonary hypertension.**

Keywords: Mitral stenosis, Mitral valve, Near systemic, Pulmonary hypertension

1. Introduction

From the sixties of the last century, when the first surgical valve replacement was published by Starr and Edward, valve surgeries, either replacement or repair, is being a highly appreciated, growing and a successful way in the treatment of valve disorders [1]. The increase in the numbers of patients who undergo Mitral valve replacement, as well as the good surgical results shifted the researches to a new horizon by focusing on searching for the risk factors, in a trial to targeting them, to decrease the expected mortality and morbidity, as well as to improve the level of postoperative quality of life for these patients [2].

By far the pulmonary hypertension is a well-known recognised risk factors in increasing mortality and morbidity for patients undergoing open heart surgery, and this forced the Euro score system calculator to integrate it as a predictor for increasing the risk of mortality and morbidity during and after surgery. But unfortunately, Euro score put the highest pulmonary artery systolic pressure (PASP) to be 55 mmHg, leaving a higher PASP to be noneffective in increasing the risk factors, this is not compatible with the researches targeting the level of

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PAP and relaying it to the linear increase in post-operative sequelae [3].

The process of increase in pulmonary artery pressure in patients affected by mitral stenosis (MS) happens due to persistent active vasoconstriction affecting peripheral pulmonary arterioles, this is reflected to an increase in its vascular resistance. The persistent of vasoconstriction causes a secondary obliterative process that affects the distal pulmonary arteriolar vascular bed. The main triggering reason of this is the back-pressure from a the stenosed Mitral orifice on the left atrial cavity (LA). This vascular changing process is affected by many variables, for example, the left atrial thin wall as well as its stiffness, this is also integrated with left atrial mechanical force associated with its rhythmic contraction, which is absent in the occurrence of atrial fibrillation, last but not least is the time of the diastole which is shortened by tachycardia. Other factors that aggravates that condition is the decrease of the compliance of ventricular muscle and pulmonary venous system, resulting in a significant rise in PA pressure (PAP), which occurs in normal persons during exercise [4].

Strangely enough, patients with severe MS, usually have different predictors to the level of increase of there pulmonary artery pressure, this is not only affected by the chronicity of MV disease or the previously discussed factors only, but personal factors also plays some role, for example, low compliance of the left atrium which in turn drive to significantly high PAP with or without left atrial dilatation. This is the reason why in spite of all patients with mitral valve disease may have some rise in their PAP, yet only around 40% of them develop a severe PAH [5].

On focusing on PAH as an independent risk factor for the in-hospital mortality in many researches, the division of patients groups according to the predominant lesion whether it is MS or Mitral regurgitation, it was noticed that patients with predominantly MS had a statistically higher in-hospital mortality when compared to patients with MR [6].

The other view is to discriminate the level of PH, and extensive subdivision of PAH into mild, moderate and severe. Literature showed a clear discrepancy regarding the postoperative results after Mitral valve surgery, as the level of PAH is highly correlated to the peri-operative early mortality, the results ranged between 16% in the patients with mild PAH, 23% in severe PAH and reaching up to 61% when the PAP was at or near systemic levels [7].

The high PAH, specially severe and near systemic, has been known as an identified risk factor, leading to poor outcome to the patients who will undergo Mitral valve surgeries, with an anticipated all cause mortality between 15 and 31%, and this is reflected on forcing most surgeons to refuse operating on this high-risk group patients [7].

But, in fact and surprisingly, on the other hand most studies reported that this severe PAH returns to normal level by time after correcting the mechanical problem causing it. This in turn emphasises the explanation for the near similar long-term survival and the same level of quality of life in those patients groups when survived early postoperative phase [8,9]. However these finding are controversial, as others published some reports showing a reduced survival and quality of life in patients having severe PAH even after being corrected by surgery [10]. The reasons for this controversy can be explained by the personal different responses of these patients to the postoperative vasodilators challenge, (defined as a decrease in mean pulmonary artery pressure (PAP) by > 10 mmHg to an absolute mean < 40 mmHg without a decrease in systemic blood pressure or cardiac output), which indicates presence of active response of the pulmonary vascular bed or what is known as vaso-activity versus fibroses noncompliant non reversible pulmonary hypertension [11].

In the last few years, many studies showed the improvement of the outcome of the patients who underwent MVR, with a recorded peri-operative mortality between only 2.3% and 10%. The improvement in the prognosis and outcomes is attributed to many factors, first, the myocardial preservation new methods and techniques, second, the new techniques in valve replacement which inquires preservation of the subvalvular apparatus, and third, the new postoperative care plans and medications which help to overcome postoperative pulmonary hypertension crisis. The new overall operative mortality rate of the high PAP patients group become nearly 9.3%. Also, the mortality rate in patients with severe PAH become 15.5%, while the patients cohort with supra-systemic PAH become 28.5%, these reflects the advancement in management plans but it also still high because of the nature of the disease [2].

On a further deeper digging in these studies, it appears that near systemic PAP increases early mortality but this decreases steadily by time, some publication reported a lesser likelihood for the ability to separate these types of patients from the heart-lung machine after the Mitral valve surgery. Postoperative myocardial failure is also a known cause of mortality due to the borderline myocardial decompensation, specially the right ventricle, in the severe pulmonary hypertension situation [2].

Trying to focus on the risk factors predicting early deaths, it was noticed that they are the prolonged ventilation time, acute kidney injury (AKI) in addition to nonpreservation of the subvalvular mitral apparatus, as well as aortic cross-clamp time [12].

The aim of this study is to put a strict protocol to try to bypass the high early mortality in this group of patients with near systemic PH with a strong evidence from literature that, on long-term survival, they have the same or nearly the same survival as patients with mild PH.

2. Patients and methods

A Prospective cohort single-centre study, was held in National Heart Institute, in the time between 2016 and 2022 on adult patients age from 18 to 60 years with isolated MS associated with grade II or less Mitral regurgitation and evidence of pulmonary hypertension >80 mmHg who will undergo Mitral valve (± tricuspid valve) surgery. The patients who receive previous bosentan or other endothelin receptor antagonist or had pulmonary disease that may affect pulmonary artery pressure or a history of pulmonary embolism are excluded from the study. Also patients with other valve disease, redo cases or ischeamic heart disease are excluded from the study. Comparison will be done with patients with mild to moderate PH, by assigning patients into 2 groups (study group, Group A or Group I (PAP> 80 and control group, Group B or group II PAP< 50), study group will follow the study protocol. Both groups will receive also the standard treatment.

2.1. Protocol of the study

Before admission patient started sildenafil citrate with a dose 50 mg twice daily two weeks before admission [13].

Special anaesthetic considerations apply to patients in order to support right ventricle. It consists of balanced anaesthetic technique, avoidance of hypoxia, hyper-carbia, smart use of vasodilator and inotrope according to individual need. Operatively antegrade intermitted warm blood Cardioplegia every 15 min is given, ACC time must be less than 40 min to maintain this, Tricuspid valve surgery, if needed, can be done on perfused beating heart, in addition to preservation of subvalvular apparatus by preserving posterior leaflet. Weaning of bypass is done with or without inotropic support, which if needed inodilators only is used,(Dobutamine or Milrinone) in addition to small dose of norepinephrine if strictly needed. Postoperatively patient remain ventilated for 12 h at least, postextubation, another 12 h is maintained under observation without weaning from inotropic support (if present), any unexplained rising in CVP measures, decrease urine output (UOP) less than 0.5 ml/kg/hour for 3 successive hours, acidosis, hypoxia or hypercarpia, elective reintubation is done immediately for an extra 24 h, and restart the process again. If the patient maintain proper hemodynamics for these 12 h a gradual weaning from the inotropes is done with monitoring of the previous parameters. During the whole ICU stay any decrease in UOP more than 3 h frusemide infusion with 40 mg/h is started and if no improvement for 6 h, an elective hemodialysis session is done. Patient will be monitored in hospital and after 6 months with primary endpoint will be the improvement of mortality, while the secondary outcome will be the improvement of NYHA class postoperative.

2.2. Statistics

The calculated sample size is 176 patients. This size achieves 80% power between new regimen treatment and standard management with β error rate of 20% and alpha error of 0.05%. Taking into consideration the expected drop-out rate assumed to be 10−15% of the total sample size; additional 24 patients will be added to the study group. The final proposed sample size was 200 subjects. These patents will be divided into two groups, a study and a control group, with ratio 1:1. The calculation depends on the average percentages of early mortality, post MVR in near systemic pulmonary hypertension, 15% and average mortality, which is 3% with MVR with mild or no PH. Continuous variables were described as mean with standard deviation. Categorical data were presented as percentage and were compared using Chi-square test. Ordinal data were described as median (interquartile range, range). All P values < 0.05 were considered as significant. The Statistical Package for Social Sciences (SPSS) version 16.0.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for analysis.

2.3. Anticipated results

The new strategies in management will lower the mortality post Mitral valve (MV) surgery with near systemic pulmonary hypertension to the same or near the post MV surgery with mild to moderate pulmonary hypertension.

3. Results

Between 2016 and 2022, these patients were collected and the study protocol was followed, any

patient who did not follow the protocol was excluded and replaced by another patient. The patients were divided to two groups, group I or A with PAP >80 and group II or B with PAP <50.

Age and sex show no difference between the two groups (38 ± 12 vs 39 ± 13) and female sex 56 vs 51. Preoperative risk factors regarding diabetes, hypertension, smoking, atrial fibrillation and COPD showed nonsignificant difference, but NYHA class was higher in group A and of course PASP (Table 1).

Operatively there was significant difference in aortic cross-clamp time between both groups as this was already involved in our study protocol and hence was expected. But bypass time showed no statistical significance (Table 2).

Regarding postoperative data, by far hours of intubation, re-intubation and length of ICU and hospital stay was longer in the first group, but on the other hand mortality and major morbidities, including new AKI or heamodyalisis, reopening for bleeding were not different. Also 6 months NYHA class were nonsignificant (Table 3).

4. Discussion

Egypt and developing countries in Africa, specially the sub saharan areas have been affected by Rheumatic heart disease (RHD) for long time, giving it to generation after the other, leading to a prevalence reaching 1−14/1000 in school-age children, and this rate increases to 7.5−51.6/1000 when echocardiography is used as a diagnostic tool [14].

The main problem of the rheumatic MS is that it targets the young productive adults during their active productive life span, specially, in the low socioeconomic countries, including Egypt, and this subsequently leads to a delay in its diagnosis and treatment. Concurrently, this makes this disease in addition of being a national health problem, an economic burden on the family, as well as the whole community [14].

Focusing on Egypt and the Egyptian population, it was astonishing to find that a preventable disease, like rheumatic heart disease, is considered the first reason of mortality among the school children. This is found to be because of more severe cardiac affection among the Egyptian children and concurrently a higher rate of heart sequelae, especially pulmonary hypertension which happens during the primary affection, or as a consequence of the healing process that causes fibrous formation leading to subsequent developing of MS. The management of this situation, is primarily surgical, but unfortunately the treatment is severely antagonised by the severe pulmonary hypertension with its short and long-term effect on the success rate of this surgical intervention [15].

In the study of Wood, which was done on 300 patients who had severe MS, it was found that high pulmonary artery pressure leading to pulmonary hypertension was found in 26% of this series, it was also found that the vascular resistance of pulmonary vasculature were above 6 woods unit [16].

The registry of the National heart institute of Egypt, the biggest centre for cardiac surgery in Egypt, stated that 44% of their cardiac surgeries per year involve Mitral valve surgery with the associated deleterious effect on pulmonary artery pressure [17].

Pulmonary hypertension (PH) related to left-sided valvular heart disease, especially MS, is considered a predictor of morbidity, as well as mortality. This happens not only during the surgery but also in the immediate period as well as the short terms results during follow-up. This is emphasised by a numerous recent and older studies that clarify that the different level of pulmonary artery pressure has disastrous effects on the short and intermediate-term outcome of Mitral valve intervention [18].

On the other hand, reports showed a continuous decrease in the pulmonary artery pressure in the postoperative period leading to nearly equal survival rate when compared with MS patients without pulmonary hypertension. This makes the choice of being reluctant in surgical management in these group of patients considered to be nonconclusive [19].

Table 1. Preoperative demographic data.

	Group A	Group B	*P* value
Age, year, mean +SD	38 ± 10.9	39.3 + 13.1	NS
Female sex, *n* (%)	46	51	NS
Diabetes, *n* (%)	4	6	NS
Hypertension, *n* (%)	11	11	NS
Tobacco use, *n* (%)	16	16	NS
Chronic lung disease, *n* (%)	0	0	NS
NYHA III/IV, *n* (%)	20	3	$P < 0.0001$
Atrial fibrillation	33	37	NS
Severe TR, *n* (%)	24	25	NS
Ejection Fraction	59.2 ± 6.5	57.9 ± 7.6	NS
PASP(mmHg)	101.2 ± 20.3	40.1 ± 4.3	$P < 0.05$
Right ventricular dimensions(cm)	2.4 ± 0.6	2.1 ± 0.8	NS

n, number; NYHA, Newyork heart association; PASP, pulmonary artery systolic pressure; SD, standard deviation; TR, Tricuspid regurgitation.

Table 2. Operative demographic data.

	Group A	Group B	*P* value
CPB time, min, mean +SD	32 ± 8.1	45 ± 6.8	$P < 0.01$
Aortic Cross clamp time, min, mean ± SD	59.3 ± 13.6	64.2 ± 20.5	NS

CPB, cardiopulmonary bypass; SD, standard deviation.

Table 3. Postoperative demographic data.

	Group A	Group B	Value
In-hospital mortality, n (%)	4	3	NS
Prolonged ICU stay (>48 h)	92	7	$P < 0.001$
Total hours ventilated postoperatively, hrs, mean +SD	18 ± 4.3	5.8 ± 2.2	$P < 0.001$
Prolonged ventilation (>24 h)	56	1	$P < 0.001$
Reintubated during hospital stay, n (%)	8	1	$P < 0.01$
Reopening for bleeding or tamponade	2	1	NS
New-onset renal failure requiring dialysis, n (%)	2	0	NS
Patient requesting dialysis	2	1	NS
Cerebrovascular accident	0	0	NS
Length of stay, days, mean +SD	12 ± 1.9	4.6 ± 0.6	$P < 0.001$

ICU, intensive care unit; SD, standard deviation.

MS patients complicated by severe PAH is noticed to have a significantly higher mortality and sequelae compared to no or mild PH ($P = 0.03$). On focusing on the causes that leads to this increase in the immediate postoperative morbidity and mortality in this cohort of patients after cardiac surgery, it was clear to be multifactorial, including red blood cell transfusion in addition to long ventilation time as well as acute kidney injury. This was attributed to the severe preoperative condition of the patient, which leads to stormy intraoperative and postoperative course which increases the mortality percentage. The question that arise at this point is how to avoid these predictors [12].

Our perspective is that to put a protocol to omit these factors and try to gain the lowest pulmonary artery pressure in the peri-operative period to bypass the immediate postoperative period safely and then, with time, this cohort of patients will continue on the same survival curve as other patients with moderate, mild and no PH.

The use of sildenafil citrate before operation is to decrease the PAP to the minimum allowed level and try to make the pulmonary vascular resistance the least before correcting the mechanical cause, in the future; the use of endothelin receptor antagonist may show a better results. Operative focusing on shortening aortic cross-clamp time and prolonged ventilation in addition to the use of inodilator in the postoperative period, is aiming to support the right ventricle till, the normally occurring, myocardial stunning and myocardial oedema subsides giving it time to regain its contractile power to face the residual high PAP which will need time to return to its normal values.

This is why there is significant difference in ACC time, ventilation time and hence its reflection on ICU stay and hospital stay between the study and the control groups.

Aggressive management of fluid balance by monitoring CVP, echocardiography and the use of the frusemide and even heamodyalisis is to prevent the entrance of the closed circle of volume overload on right ventricle, which already facing a high after load and hence its deterioration in function which sometimes become irreversible.

According to our study this protocol can be used to improve the immediate postoperative outcome of patients with MS and near systemic pulmonary hypertension.

4.1. Study limitations

The use of endothelin receptor antagonist as Bosntan is not used in this study which is now shown to have beneficial effect in this group of patients. Also due to the lack of Nitric oxide in our hospital, it was not used widely in this study.

Although the number of the patients included during this study limits its power but this will be corrected by the continuation of this study on more patients to increase the study cohort.

4.2. Conclusion and recommendations

A near systemic hypertension is not a contraindication to MV surgery, the strict following to our protocol reduced the risk of immediate mortality and morbidity following the surgery and we are expecting to improve long-term outcome as previous studies discussed. However since near systemic PAP increase the risk of mortality and morbidity during surgery and after it, Euro score and other risk score calculators must add a category for these groups of patients.

Conflict of interest

None.

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