# The Importance of Conscious Sedation for Life-Saving Valve Procedures in Patients With Rheumatic Heart Disease From Low- to Middle-Income Countries

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## ABSTRACT

**Background:** Severe valve disease, which requires intervention, remains strongly associated with mortality in patients with rheumatic heart disease. Percutaneous mitral commissurotomy (PMC) is the procedure of choice for the treatment of patients with isolated or predominantly rheumatic mitral stenosis. This procedure has been performed under sedation to avoid the potential effects of general anesthesia on intracardiac pressure measurements. However, there are limited data on sedation during PMC, especially using easily available medications in low- and middle-income countries.

**Objectives:** This study was designed to evaluate the efficacy and hemodynamic effects of conscious sedation during PMC in patients with significant mitral stenosis.

**Methods:** This study prospectively enrolled 23 patients who underwent PMC with the Inoue balloon technique for hemodynamically significant mitral stenosis. For conscious sedation, midazolam 25 $\mu$g/kg and fentanyl 1 $\mu$g/kg were administered, and 5 min after the infusion, the level of sedation was evaluated by Ramsay sedation scale. A range of invasive hemodynamic measurements, including cardiac output and pulmonary artery pressures, were recorded before and immediately after sedation.

**Results:** The mean age was 44.9 $\pm$ 10.8 years, and 19 patients (83%) were women. After sedation, the majority of patients were in categories 2 and 3 of the Ramsay sedation scale (cooperative, orientated, tranquil, and responding to commands). Oxygen saturation dropped from an average of 98.5% to 96.0% without supplementary oxygen. Left ventricular systolic pressure and central aortic pressures decreased after sedation. However, none of the other parameters changed significantly after sedation, including pulmonary artery pressures, pulmonary vascular resistance, and cardiac index.

**Conclusions:** This simple model of conscious sedation was able to promote anxiolysis, analgesia, and comfort for the procedure without serious hemodynamic effects, which can be a reasonable choice in developing countries.

Rheumatic heart disease (RHD) continues to be a serious public health problem throughout the world, especially in low- and middle-income countries, where it accounts for over a million premature deaths annually [1,2]. Percutaneous mitral commissurotomy (PMC) is the procedure of choice for the treatment of patients with severe rheumatic mitral stenosis (MS) with excellent results [3]. However, most patients with severe MS have limited access to percutaneous valve intervention [1,4]. A previous study showed that the use of percutaneous and surgical interventions was extremely low in low- and middle-income countries compared with upper-middle-income countries [1]. These disparities in the use of effective invasive interventions probably reflect differences in access to health care between countries and the cost of the procedures [5]. Therefore, strategies to provide high-quality care with affordable costs are essential to managing patients with RHD.

Percutaneous valve intervention has been performed under sedation to minimize patient discomfort induced by the prolonged invasive intervention and to avoid the potential effects of general anesthesia on intracardiac pressure measurements [3]. Although small doses may have less

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effect on hemodynamic parameters, in patients who have MS with severe pulmonary hypertension, the effect of sedation can be different. There are limited data on sedation during PMC, especially concerning sedation's impact on hemodynamic parameters in the setting of severe rheumatic MS in developing countries [6]. The choice of anesthesia technique varies according to the experience of each service, and general anesthesia or sedation may be performed [7]. Sedation techniques have evolved over the past decades resulting in more effective and titratable strategies [8]. It is important to know the hemodynamic consequences of the drugs used in daily practice in the developing world.

Midazolam and fentanyl combination has been routinely used for intravenous sedation in several procedures and both drugs are easily available in low- and middle-income countries [6,9–11]. Some studies have demonstrated the efficacy and safety of the use of remifentanil associated with hypnotic agents such as midazolam or propofol and the use of dexmedetomidine as the sole agent in conscious sedation. However, such medications may not be available in some health centers in developing countries, especially because of the cost of the medication.

Conscious sedation allows early diagnosis of cerebral embolism, which is a major complication of PMC [8]. Moreover, in patients with severe pulmonary hypertension, rapid anesthetic recovery is recommended to prevent respiratory system depression and cardiovascular complications [12,13].

This study was therefore designed to evaluate the efficacy and hemodynamic effects of conscious sedation during PMC in patients with significant rheumatic MS.

## METHODS

### Study population

The study prospectively enrolled consecutive patients who underwent PMC with the Inoue balloon technique for severe MS between October 1, 2014, and August 31, 2015. Patients were referred for PMC based on a combination of functional limitation, severity of valve obstruction, and pulmonary hypertension either at rest or during exercise [14,15]. The main indications for the procedure were significant MS and New York Heart Association functional class III/IV or class II despite treatment with diuretic agents and beta-blockers. Functional status was evaluated using the New York Heart Association classification [15].

Patients with significant aortic valve lesions (moderate or severe), pregnancy, or respiratory diseases at the time of assessment for PMC were excluded. The study protocol was approved by the Ethics and Research Committee of Federal University of Minas Gerais, and informed consent was obtained from each patient.

### Echocardiographic evaluation

A standard echocardiogram was performed prior to and within 24 h after PMC using commercially available equipment (iE33, Philips Medical Systems, Andover, Massachusetts). The measurements were obtained according to the American Society of Echocardiography [16].

Mitral valve area was measured by direct planimetry of the valve orifice in the parasternal short-axis view, and valve morphology was evaluated assessing leaflets and commissures. Peak and mean transmitral diastolic pressure gradients were measured using continuous-wave Doppler across the mitral valve in the apical 4-chamber view. The presence and severity of mitral regurgitation was evaluated as recommended [16]. The continuous-wave Doppler tricuspid regurgitant velocity was used to determine systolic pulmonary artery pressure using the simplified Bernoulli equation. Global right ventricular function was quantitatively assessed using the right ventricular myocardial performance index, peak systolic velocity at the tricuspid lateral annulus using tissue Doppler imaging, and the tricuspid annular plane systolic excursion at the right ventricular free wall obtained from 2-dimensionally guided M-mode recordings. Left atrial volume was assessed by the biplane area-length method from apical 2- and 4-chamber views. All results were based on the average of 3 measurements for patients in sinus rhythm and 5 measurements for patients in atrial fibrillation.

### Percutaneous mitral commissurotomy

Standard hemodynamic measurements of the left ventricle, left atrium, right ventricle, and pulmonary artery pressures were recorded before and immediately after sedation. Cardiac output was determined by the Fick method. Pulmonary vascular resistance was calculated using the following formula:

$$PVR = (mPAP - \text{mean } PCWP)/CO$$

PVR is pulmonary vascular resistance; mPAP is mean pulmonary artery pressure; PCWP is pulmonary capillary wedge pressure; and CO is cardiac output. PMC was performed using an antegrade trans-septal approach and the Inoue technique. After each balloon dilation, a periprocedural transthoracic echocardiogram was performed to assess mitral valve orifice area by planimetry and the degree of mitral regurgitation to determine whether further dilation was required [3].

### Local anesthesia and conscious sedation

The patients received a venous puncture with a 20-G catheter and were monitored with pulse oximetry, noninvasive blood pressure monitoring, and cardioscopy. We infiltrated 5 to 10 ml of 2% lidocaine without epinephrine in each groin before right femoral vein and left femoral artery punctures. For conscious sedation we administered midazolam 25 $\mu$g/kg and fentanyl 1 $\mu$g/kg, followed by 20 ml of saline flush, only 1 bolus of the medications was used. Data were collected before and after sedation and no subsequent boluses were administered. Two patients required supplementation with propofol boluses and were excluded from the study. Further saline infusion therapy was maintained at a speed of 20 drops/min. In obese patients, the doses were calculated by ideal body weight.

We chose the Ramsay score because it is the most used, is easily applied at the bedside, and has sufficient sensitivity and specificity to be considered a reference standard among existing sedation scores.

Considering the beginning of action of the drugs used, 5 min after the infusion, the level of sedation was evaluated by Ramsay sedation scale, as follows: 1= anxious or restless or both; 2 = cooperative, orientated, and tranquil; 3 = responding to commands; 4 = brisk response to stimulus; 5 = sluggish response to stimulus; 6 = no response to stimulus.

We avoid the use of vasopressor drugs as well as infusion of large volumes of fluids that may interfere with the calculation of the cardiac output by the formula of Fick. The patients received 300 to 400 ml of fluids considering injected saline and contrast. The procedures lasted on average of 2 to 3 h, and the patients did not have hemodynamic changes that required vasopressors.

Desaturation (oxygen saturation <90%) or respiratory rate <10 breaths/min was treated with verbal stimuli, jaw extension, and, if necessary, with supplemental oxygen (1 to 3 l/min).

## Statistical analysis

The sample size was calculated considering that a reduction of up 5% in the cardiac index after sedation would maintain hemodynamic stability. In our study, the decrease in cardiac index was 4.35% after sedation, indicating that this sample size has power to evaluate the hemodynamic changes of conscious sedation, especially related to vascular resistance and cardiac output.

Qualitative variables were analyzed by descriptive statistics. Frequency distributions were compiled and calculated using the mean ± SD of continuous variables or median (interquartile range) as appropriate. The statistical test to be used (parametric or nonparametric) in assessing variables came after analysis of the variables of normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk tests.

Hemodynamic variables before and after sedation were compared using Student's paired *t*-test or the Wilcoxon test as appropriate. All statistical analysis was performed using SPSS version 20.0 (IBM, Armonk, New York).

# RESULTS

## Baseline clinical characteristics

A total of 25 patients who underwent PMC were initially were initially enrolled. However, 2 patients who required supplementation with propofol boluses during the procedure were excluded, leaving 23 patients for the final analysis. The mean age was 44.9 ± 10.8 years, and 19 patients (83%) were women. The majority of the patients (78%) were in New York Heart Association functional classes II and III. Baseline clinical characteristics of the study population are summarized in Table 1.

Diuretics and beta-blockers were the most frequently used medications (78%). Sixteen patients (70%) were on warfarin due to previous embolic events or atrial fibrillation. Patients presented with severe MS with mean mitral valve area of 0.97 $cm^2$, mean transvalvular gradient of 12.5 mm Hg, and mean systolic pulmonary artery pressure of 54 mm Hg. Although the majority of the patients were in sinus rhythm, left atrial dimensions were severely increased with mean left atrial volume index of 58 $ml/m^2$.

**TABLE 1.** Baseline characteristics of the study population

| Variables | Patients |
|---|---|
| Clinical data | |
| Age, yrs | 44.9 ± 10.8 |
| Female | 19 (83) |
| Body surface area, $m^2$ | 1.67 ± 0.2 |
| Body mass index, $kg/m^2$ | 25.9 ± 6.7 |
| NYHA functional class | |
| II | 7 (30) |
| III | 11 (48) |
| IV | 5 (22) |
| Atrial fibrillation | 5 (22) |
| Heart rate, beats/min | 76.9 ± 11.8 |
| Systolic/diastolic blood pressures, mm Hg | 115.4 ± 10.2/77.8 ± 9.3 |
| Medications | |
| Diuretics | 17 (74) |
| Beta-blockers | 18 (78) |
| Anticoagulants | 16 (70) |
| Echocardiographic parameters | |
| Left ventricular ejection fraction, % | 61.5 ± 8.4 |
| Left atrial diameter, mm | 49.3 ± 5.1 |
| Left atrial volume index, $ml/m^2$ | 58.3 ± 13.5 |
| Mitral valve area by planimetry, $cm^2$ | 0.97 ± 0.2 |
| Transvalvular mitral peak gradient, mm Hg | 20.1 ± 6.7 |
| Transvalvular mitral mean gradient, mm Hg | 12.5 ± 5.4 |
| Pulmonary artery systolic pressure, mm Hg | 54.4 ± 22.1 |
| Peak systolic velocity at the tricuspid annulus, cm/s | 9.5 ± 2.0 |
| Tricuspid annular motion, mm | 16.2 ± 4.7 |
| Right ventricular myocardial performance index | 0.47 ± 0.3 |

Values are mean value ± SD or n (%).
NYHA, New York Heart Association.

**TABLE 2.** Hemodynamic characteristics of patients with MS undergoing PMC before and after sedation

| Hemodynamic Variables | Baseline | After Sedation | p Value |
|---|---|---|---|
| Heart rate, beats/min | 73.3 ± 11.1 | 69.1 ± 11.2 | 0.213 |
| Oxygen saturation | 98.5 ± 1.9 | 96.0 ± 3.2 | 0.006 |
| LV systolic pressure, mm Hg | 125.1 ± 21.6 | 109.4 ± 18.4 | <0.001 |
| LV end-diastolic pressure, mm Hg | 11.1 ± 3.2 | 10.6 ± 3.2 | 0.368 |
| Aortic systolic pressure, mm Hg | 120.7 ± 21.9 | 104.7 ± 15.3 | <0.001 |
| Aortic diastolic pressure, mm Hg | 73.1 ± 15.3 | 66.9 ± 12.4 | 0.091 |
| Aortic mean pressure, mm Hg | 89.7 ± 16.4 | 80.0 ± 12.5 | 0.008 |
| Right atrial pressure, mm Hg | 6.0 ± 2.7 | 6.1 ± 2.3 | 0.794 |
| Systolic PAP, mm Hg | 49.1 ± 28.2 | 53.2 ± 25.6 | 0.307 |
| Diastolic PAP, mm Hg | 25.9 ± 14.7 | 25.4 ± 18.5 | 0.645 |
| Mean PAP, mm Hg | 35.3 ± 19.6 | 34.6 ± 20.3 | 0.786 |
| Left atrial pressure, mm Hg | 22.0 ± 10.5 | 20.4 ± 10.2 | 0.334 |
| PVR index, dynes·s/cm$^{-5}$/m$^2$ | 431 (86–644) | 420 (189–634) | 0.678 |
| SVR index, dynes·s/cm$^{-5}$/m$^2$ | 2,953 (2,142–4,275) | 2,787 (2,455–3,737) | 0.508 |
| Cardiac output, l/min | 3.7 ± 0.9 | 3.6 ± 0.8 | 0.976 |
| Cardiac index, l/min/m$^2$ | 2.3 ± 0.5 | 2.2 ± 0.6 | 0.789 |

Data are expressed as the mean value ± SD or median (interquartile range).
LV, left ventricular; MS, mitral stenosis; PAP, pulmonary artery pressure; PMC, percutaneous mitral commissurotomy; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance.

## Effects of sedation on hemodynamic measurements before PMC

After administration of midazolam and fentanyl, the Ramsay sedation scale was assessed. The majority of patients were in the categories 2 and 3—cooperative, orientated, tranquil, and responding to commands. The hemodynamic parameters before and after sedation are presented in Table 2. The heart rate remained unchanged, whereas oxygen saturation dropped from an average of 98.5% to 96.0% without supplementary oxygen. Left ventricular systolic pressure and central aortic pressures decreased after sedation. However, none of the other parameters changed significantly after sedation, including pulmonary artery pressures, pulmonary vascular resistance, and cardiac index (Figure 1).

## Outcome data

PMC was performed without major complications in all patients. The sizes of the Inoue balloon ranged from 23 to 28 mm, mean of 25 mm with a mean volume of 1.5 ml. In 8 patients (35%), only 1 balloon inflation was necessary, whereas in the remaining cases, 2 or more dilations were required to have a final mitral area higher than 1.5 cm$^2$. Only 1 patient developed severe mitral regurgitation immediately after the procedure.

PMC resulted in a significant increase in mitral valve area from 0.9 ± 0.3 to 1.7 ± 0.2 cm$^2$ ($p < 0.001$), a decrease in mean gradient from 12.9 ± 5.5 to 5.1 ± 1.6 mm Hg ($p < 0.001$) and a decrease in mean pulmonary pressure from 35.3 ± 19.6 to 28.3 ± 10.4 mm Hg ($p = 0.021$). Similarly, left atrial pressure decreased from 22.3 ± 10.5 to 15.6 ± 5.1 mm Hg ($p = 0.022$) following the procedure. The cardiac index increased from 2.3 ± 0.5 to 2.5 ± 0.7 mm Hg ($p = 0.032$).

At the end of the procedure, the patients were conscious and hemodynamically stable and remained in the anesthesia recovery room for an average time of 30 to 60 min and then were referred to the ward. Only 1 patient who developed severe mitral regurgitation required intensive care unit admission.

## DISCUSSION

The present study examined potential hemodynamic and respiratory impact of conscious sedation in patients with MS undergoing PMC. A combination of midazolam and

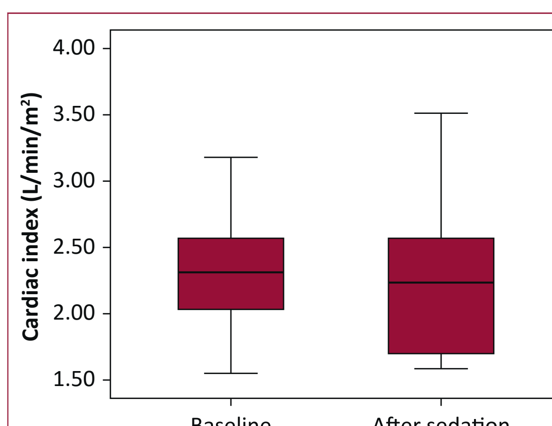


**FIGURE 1. Cardiac index of the patients with severe mitral stenosis before and after sedation showing no significant changes.**

fentanyl had no impact on all hemodynamic parameters assessed, including cardiac index and pulmonary vascular resistance. These affordable medications can be used to promote analgesia and comfort in patients with RHD from low- and middle-income countries.

Midazolam, a benzodiazepine used for anxiolysis, amnesia, and conscious sedation, reaches its peak effect within 2 to 3 min. It also has rapid onset and offset compared with other benzodiazepines, and its respiratory and cardiovascular effects are well known [10]. Midazolam produces dose-related central respiratory system depression and modest decrease in arterial blood pressure resulting from a decrease in systemic vascular resistance [10,12]. Fentanyl provides analgesia, which is a vital component of sedation and anesthesia. Like midazolam and other anesthetic drugs, fentanyl produces dose-related effects in the respiratory and cardiovascular systems [10,12]. Conscious sedation has been increasingly used in various surgical procedures, and 1 can perform neurological evaluations intraoperatively and immediately after the procedure [11,17–19]. The best agents for conscious sedation for invasive procedures are not defined [11,20–22]. Anesthetic agents such as propofol and dexmedetomidine have been used alone or in association with fentanyl, but any proposed scheme has advantages and disadvantages. Propofol has fast onset, fast offset, and deeper sedation, but it has a narrow therapeutic index. The most common adverse effects of dexmedetomidine are hypotension and bradycardia, both of which are undesirable effects on patients with borderline cardiac function [21].

Although the association of fentanyl and midazolam may increase the risk of respiratory depression, in this study, the patients were able to respond to verbal commands and improve on their own respiratory drive, improving peripheral oxygen saturation without requiring supplemental oxygen, and had minor changes of hemodynamic values.

PMC is now considered to be the procedure of choice for treatment of patients with severe rheumatic MS [3]. However, general anesthesia may induce a reduction in peripheral vascular resistance and heart rate leading to decreased cardiac output. An increasing number of centers begin to perform the procedure under deep sedation with good results. There is an increasing amount of data supporting the safety of performing hemodynamic procedures under conscious sedation [23,24]. However, there is a lack of studies on sedation during percutaneous procedures in low- to middle-income countries.

In the present study, we demonstrated that a combination of midazolam and fentanyl achieved deep sedation, without significant changes in the hemodynamic parameters, allowing spontaneous ventilation to be maintained, which reduces the period of hospital stay and costs. Therefore, percutaneous mitral procedure may be successfully conducted under these medications in patients with RHD from limited-resource regions.

### Study limitations

This study compared hemodynamic variables before and after sedation with only a combination of anesthetic agents. Further studies are required to evaluate and compare this drug combination with other models of conscious sedation and general anesthesia in patients undergoing PMC. There is a lack of publications that support and enable other inferences on sedation in this specific procedure.

## CONCLUSIONS

We conclude that this simple model of conscious sedation was able to promote anxiolysis, analgesia, and comfort for the procedure without serious hemodynamic effects, which can be a reasonable choice in developing countries. However, it does not replace the need for improved infrastructure, equipment, and health supplies.

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