# Milrinone Acts as a Vasodilator But Not an Inotrope in Children After Cardiac Surgery—Insights From Wave Intensity Analysis

Sarfaraz Rahiman, FCICM[1,2]; Remi Kowalski, PhD[3]; Sit Yee Kwok, FHKAM (pediatrics)[4]; Sunit Matha, FCICM[5]; Bryn Jones, FCSANZ[3]; Joseph J. Smolich, MB BS, PhD[6,7]; Jonathan P. Mynard, PhD[3,6,7,8]; Warwick Butt, FJFICM[9]; Johnny Millar, PhD[9]

**Objectives:** Milrinone is an inodilator widely used in the postoperative management of children undergoing cardiac surgery. The literature supporting its inotropic effect is sparse. We sought to study the effect of milrinone on the vasculature and its effects on the ventricular function using wave intensity analysis. We also intended to evaluate the feasibility of using wave intensity analysis by the bedside.

**Design:** prospective single-center observational study.

**Setting:** PICU of a tertiary children's hospital.

**Patients:** Children (< 18 yr) admitted to PICU following cardiac surgery who required to be commenced on a milrinone infusion.

**Interventions:** Echocardiography and Doppler ultrasound assessments for wave intensity analysis were performed prior to commencing milrinone and 4–6 hours after milrinone infusion.

**Measurements and Main Results:** Wave intensity analysis was successfully performed and analyzed in 15 of 16 patients (94%). We identified three waves—a forward compression wave, backward compression wave, and forward decompression wave. The waves were described with their cumulative intensity and wave-related pressure change. There was a 26% reduction in backward compression wave cumulative intensity following the introduction of milrinone. Other variables (backward compression wave cumulative intensity/forward compression wave cumulative intensity ratio, backward compression wave wave-related pressure change, backward compression wave wave-related pressure change/forward compression wave wave-related pressure change ratio) consistent with vasodilation also decreased after milrinone. It also decreased the vascular wavespeed by 7.1% and increased the distensibility of the vessels by 14.6%. However, it did not increase forward compression wave cumulative intensity, a variable indicating the systolic force generated by the ventricle. Forward decompression wave cumulative intensity indicating ventricular early diastolic relaxation also did not change.

**Conclusions:** In a cohort of children recovering in PICU after having undergone cardiac surgery, we found that milrinone acted as a vasodilator but did not demonstrate an improvement in the contractility or an improved relaxation of the left ventricle as assessed by wave intensity analysis. We were able to demonstrate the feasibility and utility of wave intensity analysis to further understand ventriculo-vascular interactions in an intensive care setting. (*Crit Care Med* 2020; 48:e1071–e1078)

**Key Words:** congenital heart disease; inotropy; milrinone; pediatric intensive care; vasodilation; wave intensity analysis

Milrinone, a phosphodiesterase III inhibitor, has been shown to reduce the occurrence of low cardiac output syndrome (LCOS) following surgery for congenital heart disease in children (1). It has been demonstrated to decrease filling pressures, decrease systemic and pulmonary arterial pressures by the virtue of vasodilation (1–5). However, it remains unclear whether the observed increase in cardiac output in these studies is a by-product of vasodilation alone rather than an increase in contractility. Studies that have attempted to specifically examine the role of milrinone in providing positive inotropy independent of vasodilation

[1]Department of Paediatric Intensive Care, Queensland Children's Hospital, Brisbane, Qld, Australia.

[2]School of Medicine, University of Queensland, Brisbane, Qld, Australia.

[3]Department of Cardiology, Royal Children's Hospital, Melbourne, Parkville, VIC, Australia.

[4]Department of Paediatric Cardiology, Queen Mary Hospital, Hong Kong.

[5]Department of Paediatric Intensive Care, Monash Children's Hospital, Melbourne, VIC, Australia.

[6]Heart Research, Murdoch Children's Research Institute, Melbourne, VIC, Australia.

[7]Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia;

[8]Department of Biomedical Engineering, University of Melbourne; Melbourne, VIC, Australia.

[9]Department of Paediatric Intensive Care, Royal Children's Hospital, Melbourne, VIC, Australia.



**DOI: 10.1097/CCM.0000000000004622**

have yielded disparate results due to dissimilar methodology (3, 6–10).

Traditional methods like echocardiography used to evaluate cardiac function by the bedside are unable to assess vasodilation independent inotropic effects of vasoactive agents (11, 12). Echocardiographic estimation is further limited in the postoperative cardiac patient due to a lack of adequate sonographic windows. Furthermore, the current gold-standard to estimate inotropy involves invasive intracardiac measurements to derive ventricular pressure-volume loops (12, 13). A potential and as yet unapplied approach for teasing out the mechanisms underlying the clinical effects of milrinone is wave intensity analysis (WIA). WIA describes ventriculo-vascular interactions based on the energy flux of pressure-velocity waves that are generated by ventricular contraction (forward waves) and are partially reflected in the vascular network (backward waves) (14–17). The three key waves identified after a single systolic contraction are as follows:

- forward compression wave (FCW) which is a pressure- and velocity-increasing wave caused by ventricular ejection,
- backward compression wave (BCW) is a pressure-increasing, velocity-decreasing wave caused by reflections from downstream in the systemic vascular tree, and
- forward decompression wave (FDW) is a pressure- and velocity-decreasing wave caused by active ventricular untwisting (related to cardiac early diastolic function) and the accompanying deceleration of the column of blood in the aorta.

WIA also has a distinct advantage with respect to the quality of image acquisition over conventional techniques such as echocardiography as the images can be noninvasively acquired at a site away from the operative site (common carotid artery).

We conducted this study to assess the contribution of milrinone to left ventricular (LV) contractility and relaxation and its effect on vascular resistance. We also assessed the feasibility of using WIA by the bedside in children after cardiac surgery. Use of WIA in the pediatric intensive care setting has not been reported in the literature and to the best of our knowledge, there are no studies using WIA to assess the effects of milrinone.

## MATERIALS AND METHODS

The study was undertaken in the pediatric cardiac ICU of a tertiary referral pediatric hospital and was approved by the human research ethics committee of the Royal Children's Hospital, Melbourne. Patients less than 18 years old admitted to PICU after cardiac surgery in whom a clinical decision had been made by the treating clinician to start milrinone were eligible for inclusion. Children on extracorporeal life support were excluded. Written informed consent was obtained from parents or guardians of children prior to study enrolment.

Milrinone was commenced in these patients in accordance with local unit protocol, which suggests its use as a second-line therapy in suspected myocardial dysfunction and preserved blood pressure or if dobutamine causes unacceptable tachycardia (18). Milrinone infusion was generally started at 0.5 micrograms/kg/min without a loading dose. Decisions regarding subsequent titration of milrinone infusion and/or other vasoactive agents were entirely at the discretion of the treating clinician. Standard monitoring and care were continued as per usual local PICU practice.

Clinical information regarding diagnosis and details of the surgery and cardiopulmonary bypass (CPB) were extracted from the patient information database. Routine postoperative clinical observations were recorded from the bedside charts for an 8-hour study epoch (2 hr before the milrinone infusion to 6 hr after the infusion was commenced). Hemodynamic monitoring data were averaged for 2 hours before the commencement of milrinone and presented as "pre" values. The subsequent 6 hours were averaged to provide the "post" milrinone readings.

Before the commencement of milrinone, a transthoracic focused echocardiogram was performed which served as the baseline premilrinone study. This echocardiogram assessed two indices of ventricular function using strain imaging techniques (global strain rate [SR] and ejection fraction [EF]). Imaging for WIA was performed in the same sitting. These studies were performed by either one of the two primary investigators trained in both echocardiography and image acquisition for WIA using a iE33 echocardiography machine (Koninklijke Philips, Amsterdam, The Netherlands). The second set of studies (echocardiography and WIA) was performed 4–6 hours after starting the milrinone infusion. All images were checked for quality and accuracy by senior pediatric cardiologists specializing in the modality (strain imaging using QLAB cardiac analysis cardiovascular ultrasound quantification software [Philips] [B.J.]; WIA [R.K.]).

### WIA

For the purpose of image acquisition for WIA, a vascular probe was used to examine the common carotid artery. At a sweep speed of 100 mm/s, a 5–10 beat cine echo loop of carotid artery flow velocity was acquired using pulsed-wave Doppler, with the sampling gate extended over two thirds of the vessel diameter, with an angle of insonation at less than 60° in accordance with published guidelines (19). Subsequently, a 5–10 beat cine echo loop of carotid artery diameter was recorded with M-mode echocardiography at the same site, and the invasive blood pressure at the time was recorded.

These images were then exported from the echo analysis software as individual image files, with each individual beat cropped to the peak of the electrocardiogram R-wave, and each image cropped to the length of the shortest R-R interval in the series (**Figs. 1** and **2**). Using custom-developed software, automated edge-detection, ensemble averaging, and smoothing of signals with a Savitzky-Golay filter (20) were performed. As central arterial distension and invasively measured pressure waveforms correlate closely in systole (21, 22), the arterial diameter profile was converted to a pressure waveform via a two-point calibration using systolic and diastolic arterial pressures. The resulting averaged pressure/diameter and velocity waveforms were saved into a text file and imported into customized programmable analysis software (Spike2, Cambridge,

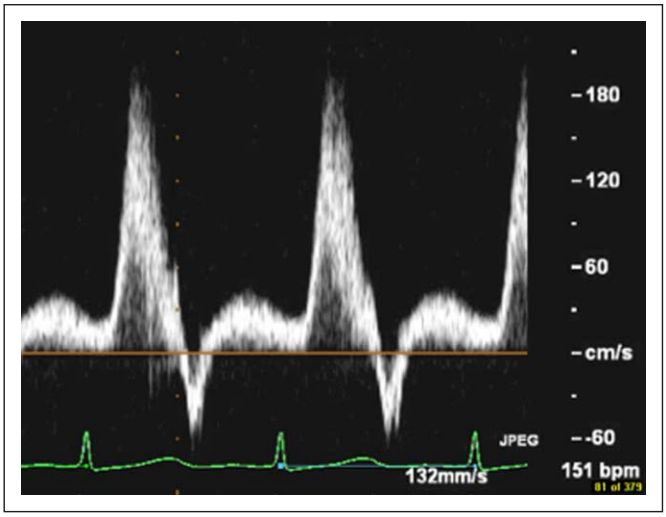


**Figure 1.** A still image of pulsed-wave Doppler of common carotid artery flow velocity. bpm = beats/min.

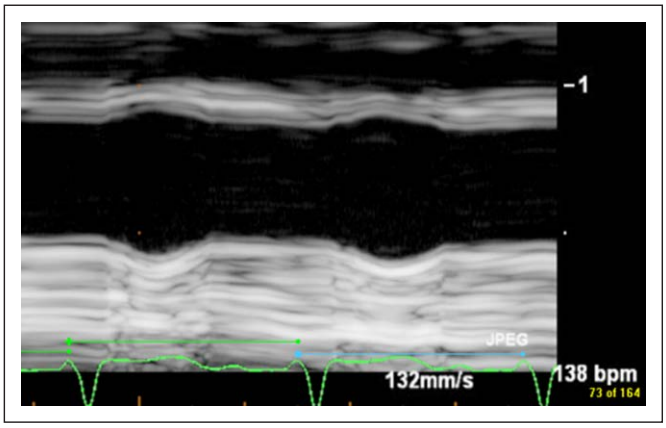


**Figure 2.** M mode of the common carotid artery. bpm = beats/min.

United Kingdom) for WIA. Mean velocity was then estimated from the maximum velocity (Doppler spectral envelope) using the scaling factors α and β described in our recent work (23). Net WIA was calculated as the instantaneous product of the rates of change in pressure and velocity (24–26) and separated into forward and backward components using wavespeed calculated with the ln(D)P loop method (23). As per convention, "forward-running" and "backward-running" waves propagated away from and toward the ventricle respectively, whereas "compression" and "decompression" waves increased and decreased pressure respectively (27). Wave size was quantified via wave area (cumulative intensity [CI]), obtained by integrating WI over wave duration. Forward and backward components of pressure were obtained by integrating pressure differentials, and wave-related pressure change (ΔP) obtained as the pressure difference measured between the start and end of the wave (28). Three waves were studied—FCW and FDW originating from the heart and BCW originating from the vasculature (17) (**Fig. 3**). Using invasively measured arterial pressures, arterial compliance was calculated as (diameter difference)/(pulse pressure) and distensibility as (diameter difference)/(diastolic diameter × pulse pressure) (29).

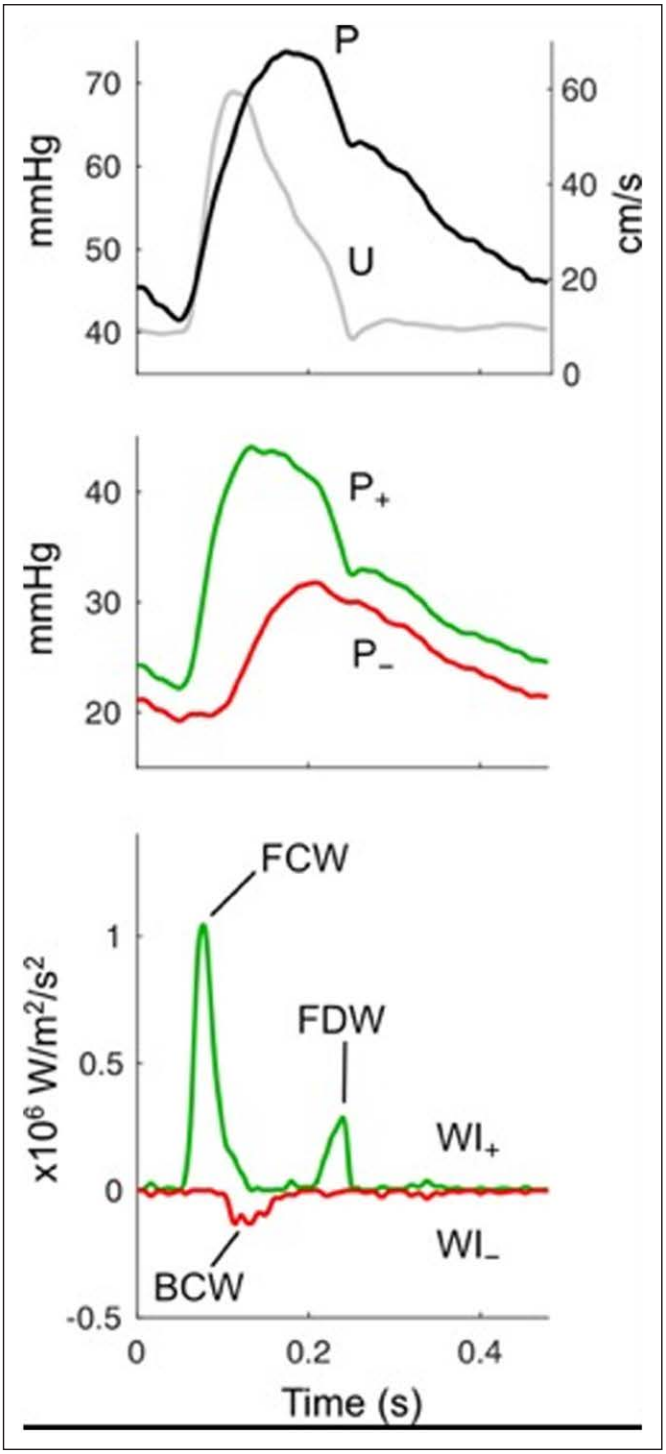


**Figure 3.** Example of acquired pressure (P), velocity (U), forward and backward components of pressure (P+ and P–, respectively) and forward and backward components of wave intensity (WI+ and WI–, respectively). The forward compression wave (FCW), backward compression wave (BCW), and forward decompression wave (FDW) are also indicated.

## Statistical Analysis

The clinical, echocardiographic, and WIA results were exported into a Microsoft Excel spreadsheet, and statistical analysis was conducted using IBM SPSS statistics Version 23 (IBM, Armonk, NY). Data were expressed either as mean (SD) or median (interquartile range [IQR]). Data were checked for normality

using the Shapiro-Wilk test. Logarithmic transformation was used to transform data with nonnormal distribution prior to testing for statistical significance. The paired pre- and postmilrinone values were compared using a two-tailed paired *t* test or the Wilcoxon signed-rank test, depending on data distribution.

## RESULTS

During the study period from November 2014 to July 2015, there were 16 eligible patients in whom consent was obtained for participation in the study. Of the 16 patients, 10 (63%) received only milrinone with no other vasoactive drugs, and six patients (37%) had milrinone added to existing vasoactive infusions (dobutamine, adrenaline, noradrenaline, glyceryl trinitrate, sodium nitroprusside), the doses of which were not changed between the pre and post milrinone assessments.

Clinical data were available for all 16 patients. Pre and post milrinone WIA datasets considered of sufficient quality for further analysis were available for 15 of 16 patients (94%). Owing to inherent difficulties in transthoracic echocardiography following cardiac surgery, strain SR was only available in 11 patients (69%), and nine patients (56%) had observations to compute EF.

Patient characteristics have been described in **Table 1**. The median age of the population was 101 days (IQR, 28–297 d). Nine patients (56%) were male, and four patients (25%) had single ventricle physiology. Two patients had small residual ventricular septal defects. Two others had moderate valvular regurgitation, and one patient had severe atrioventricular valve regurgitation (Table 1). The median time between the pre and post milrinone WIA/echocardiographic studies was 4 hours 40 minutes (IQR [4 hr 15 min–5 hr 11 min]). A median time of 71 hours (IQR, 21–254 hr) had elapsed after CPB when milrinone infusion was commenced. Fifteen of 16 patients (94%) had milrinone infusion at a rate of 0.5 µg/kg/min, and one patient had 0.75 µg/kg/min.

### Clinical and Echocardiographic Variables

There was no change in heart rate following the administration of milrinone (**Table 2**). Systolic blood pressure (SBP) and mean arterial pressure (MAP) decreased, but the diastolic blood pressure did not change. A small and borderline reduction was noted in central venous pressure (CVP) after milrinone. Although EF and SR did not change, there was a significant decrease in serum lactate following the commencement of milrinone.

### WIA Variables

There was a 26% reduction in BCW CI following the introduction of milrinone (Table 2). However, no appreciable change was demonstrated in FCW CI and FDW CI. The BCW CI/FCW CI ratio reduced by 27% following administration of milrinone, but the FDW CI/FCW CI ratio did not change. Similarly, a significant reduction of 23% occurred in BCW ΔP with no change noted in FCW ΔP and FDW ΔP. BCW ΔP/FCW ΔP ratio decreased by 18% after milrinone infusion, but the FDW ΔP/FCW ΔP ratio did not change.

### Vascular Function Variables

Milrinone decreased the carotid wavespeed (c) by 7%. Carotid distensibility increased by 15%, but vascular compliance demonstrated no significant change after administration of milrinone (Table 2).

## DISCUSSION

In our subset of patients in PICU recovering after cardiac surgery, milrinone produced vasodilation as evidenced by clinical, WIA, and vascular function variables. This is supported by a decrease in blood pressure (SBP, MAP) and CVP, decreased local wavespeed, and increased distensibility of the vessels. Other WIA variables indicative of vascular tone also demonstrated similar changes. Of note, there was no improvement in the ventricular systolic force or early diastolic relaxation.

### Feasibility

Ultrasound data required for WIA were successfully obtained in all of the enrolled patients, with no reportable adverse events related to the scans. Of note, due to challenges with postoperative transthoracic imaging, EF could only be obtained in 10 of 16 (63%) and SR in 12 of 16 (75%). The image quality for WIA was optimal and deemed suitable for further assessment in 15 of 16 (94%). Although WIA has been used for the interrogation of various vasoactive agents, it has been using traditional invasive monitoring techniques. WIA has been used for the interrogation of various vasoactive agents using traditional laboratory–based invasive monitoring techniques (24, 26, 30) and noninvasive methods in a clinical setting (23, 31–35). We were able to show not only that reliable data can be acquired noninvasively but also that it can be done by the bedside in a clinical setting in children. However, we do acknowledge that further post processing analysis requires sophisticated software and expertise. As far as we are aware, this is the first study to have reported ultrasound-based WIA acquired from the bedside in a clinical setting in children. Although currently a research tool due to the need for specialized software and expertise, our study indicates a potential for future clinical application.

### Effect of Milrinone on Vasculature

It has been described that the total energy, or "CI" of BCW and the corresponding pressure change (BCW ΔP) decreases with vasodilation and vasoconstriction elicits the opposite effect (30, 32, 36, 37). BCW CI/FCW CI and BCW ΔP/FCW ΔP are ratios of vascular reflections indexed to the corresponding FCW generated during a single systolic contraction.

Following milrinone, there was a significant reduction in every single WIA variable indicating vasodilation (BCW CI, BCW CI/FCW CI, BCW ΔP, and BCW ΔP/FCW ΔP). Milrinone also decreased the wavespeed and increased the distensibility of the examined vessels. Milrinone has consistently performed as a potent vasodilator in multiple experimental and animal studies (38, 39). Clinical studies in humans (2, 9) have demonstrated a consistent dose-dependent vasodilator effect. We found that milrinone reduced the SBP, MAP, and CVP. This

**TABLE 1. Demographic and Diagnostic Details of the Study Population**

| No | Age, mo | Diagnosis: Operation | Wave Intensity Analysis | Milrinone Commencement (Time [hr] After Cardiopulmonary Bypass) | Residual Lesions Post Surgery | Valvar Stenosis or Regurgitation |
|---|---|---|---|---|---|---|
| 1 | 13.5 | Dilated cardiomyopathy: s/p heart transplant | + | 44.6 | – | – |
| 2 | 0.9 | Double outlet right ventricle, VSD, hypoplastic arch: s/p arterial switch, arch repair | + | 524.2 | – | Moderate neo-PR |
| 3 | 6.2 | Double inlet left ventricle, TGA, VSD: s/p bidirectional cavopulmonary circulation | + | 8.4 | – | – |
| 4 | 0.9 | HLHS: s/p Norwood stage 1 | + | 606.9 | – | Severe atrioventricular valve regurgitation |
| 5 | 0.4 | Coarctation of aorta, VSD: s/p arch repair, VSD closure | – | 64.5 | – | – |
| 6 | 2.1 | Atrio VSD: s/p repair | + | 196.1 | – | – |
| 7 | 4.6 | AS: s/p AS repair, redo AS repair; s/p Ross procedure | + | 77.3 | – | Mild neo-AR, mild PR, mild MR |
| 8 | 6.0 | TOF: s/p repair | + | 32.8 | – | Free PR |
| 9 | 1.7 | TGA, VSD, left ventricular outflow tract obstruction: s/p Blalock Taussig shunt, atrial septectomy | + | 3.6 | – | Mild MR |
| 10 | 51.7 | HLHS: s/p Fontan; s/p Fontan takedown | + | 457 | – | Mild TR |
| 11 | 0.3 | Total anomalous pulmonary venous drainage: s/p repair | + | 202.7 | – | – |
| 12 | 212.2 | TGA, VSD, pulmonary stenosis: s/p REV procedure; s/p mitral valve repair | + | 233.5 | – | Moderate MR |
| 13 | 8.5 | TOF: s/p repair | + | 313.9 | Small residual VSD | Mild MR, mild TR |
| 14 | 0.2 | TGA, VSD: s/p arterial switch operation, VSD closure | + | 5.3 | Small residual VSD | – |
| 15 | 202.9 | Dilated cardiomyopathy: s/p left ventricular assist device; s/p heart transplant | + | 25.5 | – | Mild TR |
| 16 | 0.9 | VSD, atrial septal defect: s/p repair | + | 3.1 | – | Mild TR |

AR = aortic regurgitation, AS = aortic stenosis, HLHS = hypoplastic left heart syndrome, MR = mitral regurgitation, PR = pulmonary regurgitation, s/p = status post, TGA = transposition of great arteries, TOF = Tetralogy of Fallot, TR = tricuspid regurgitation, VSD = ventricular septal defect.

+Wave intensity analysis (WIA) data available.

–WIA data unavailable.

Dashes indicate data not applicable.

has been noted in clinical studies with similar populations to ours (3). Although this was predictable, it also highlights the fact that our patients did have hemodynamic changes owing to the action of milrinone. We allowed at least 4 hours (median time 4 hr 46 min) after milrinone infusion to conduct the postmilrinone study. This would allow for a milrinone infusion without a loading dose to attain similar plasma levels, and consequent hemodynamic effects, to one that is commenced after a loading dose (40).

### Effect of Milrinone on LV Systolic Function

FCW CI and the corresponding pressure change FCW ΔP are sensitive to inotropes and provide insights into LV contractility. An exponential relationship has been reported between FCW CI and LV maximal rate of rise of pressure ($dP/dt_{max}$) (26). In our study, milrinone produced no change in FCW CI or FCW ΔP, whereas conventional inotropes like dobutamine have been shown to increase FCW CI intensity, with up to an 18-fold increase reported in some studies (25, 26, 37).

**TABLE 2. Clinical, Echocardiographic, Wave Intensity Analysis, and Vascular Function Variables**

| Variables | Pre Milrinone | Post Milrinone | *p* |
|---|---|---|---|
| Clinical variables, mean (SD), $n = 16$ | | | |
| Heart rate (per min) | 138 (21) | 143 (21) | 0.18 |
| Systolic blood pressure (mm Hg) | 87 (13) | 80 (16) | 0.02 |
| Diastolic blood pressure (mm Hg) | 44 (7) | 42 (6) | 0.15 |
| Mean arterial pressure (mm Hg) | 60 (8) | 56 (7) | 0.04 |
| Central venous pressure (mm Hg) | 10 (5) | 9 (5) | 0.05 |
| Lactate (mmol/L) $n = 14$ | 1.8 (0.9) | 1.5 (0.8) | 0.01 |
| Echocardiographic variables, mean (SD) | | | |
| Ejection fraction | 54.4 (12.2) | 57.2 (14.7) | 0.28 |
| $n = 10$ | | | |
| Strain rate | 20.3 (5.9) | 21.1 (6.4) | 0.18 |
| $n = 12$ | | | |
| Wave intensity analysis variables, mean (SD), $n = 15$ | | | |
| FCW CI ($10^3$.W/m$^2$/s) | 54.8 (70.1) | 50.3 (30) | 0.93 |
| BCW CI ($10^3$.W/m$^2$/s) | 18.2 (20) | 13.4 (11.6) | **0.04** |
| FDW CI ($10^3$.W/m$^2$/s) | 24.2 (41.9) | 17.6 (11.3) | 0.64 |
| BCW CI/FCW CI ratio | 0.37 (0.1) | 0.27 (0.1) | **0.04** |
| FDW CI/FCW CI ratio | 0.37 (0.2) | 0.37 (0.2) | 0.40 |
| FCW ΔP (mm Hg) | 27.3 (16.5) | 24.9 (9.9) | 0.40 |
| BCW ΔP (mm Hg) | 18.1 (9.9) | 13.9 (7.2) | **< 0.05** |
| FDW ΔP (mm Hg) | 18.4 (18.3) | 17.4 (9.9) | 0.57 |
| BCW ΔP/FCW ΔP ratio | 0.67 (0.1) | 0.55 (0.1) | **0.01** |
| FDW ΔP/FCW ΔP ratio | 0.60 (0.2) | 0.68 (0.2) | 0.13 |
| Vascular function variables, mean (SD), $n = 15$ | | | |
| Local wavespeed (m/s) | 4.2 (0.7) | 3.9 (0.8) | **0.05** |
| Compliance (μm/mm Hg) | 14.7 (6.9) | 16.2 (6.6) | 0.26 |
| Distensibility (1/mm Hg) | 0.41 (0.1) | 0.48 (0.2) | **0.04** |

BCW = backward compression wave, CI = cumulative intensity, FCW = forward compression wave, FDW = forward decompression wave, ΔP = wave-related pressure change, W/m$^2$/s = rate of energy flux per unit area per second (units to describe intensity of a wave).
See text for definitions of compliance and distensibility.
Boldface values indicate statistical significance.

Although milrinone has been demonstrated to decrease filling pressures, systemic and pulmonary arterial pressures, and either prevent LCOS or increase cardiac output (1–3), studies that have questioned the relative contribution of inotropy are few (3, 6). The literature supporting milrinone as an agent that increases systolic function independent of benefits achieved as a result of its vascular actions is sparse. It has not consistently increased the systolic force, especially when tested in load-independent conditions (8). Axelsson et al (41) noticed that in anesthetized pigs after induction of ischemic LV dysfunction, milrinone increased the $dP/dt_{max}$ when compared with baseline. Similar results with an increased $dP/dt_{max}$ were obtained in other studies (42). However, a load-independent index "preload recruitable LV stroke work" (PRSW) did not improve significantly (41). Royse et al (38) also found no significant increase in PRSW derived from ventricular pressure-volume loops.

Stocker et al (7), studied ventriculo-vascular coupling in piglets after the experimental induction of CPB. Milrinone prevented an increase in LV afterload but did not improve myocardial contractility. Other animal studies with largely dissimilar

methodology have reported conflicting results when examining the indices of ventricular systolic function after milrinone (42–44). Although WIA analysis is not load-independent, our findings that milrinone failed to increase the FCW CI contribute to the body of literature questioning its inotropic effects.

One of the considerations to be discussed in a study involving milrinone use in neonates and young children is the age-related differences in the effects of milrinone on this population. The inotropic effects of milrinone are either minimal or absent when used in newborn animals when compared with its effects on older animals (45, 46). There have been no studies conducted in humans to corroborate these findings.

### Effect of Milrinone on LV Early Diastolic Function

An improvement in LV early diastolic performance results in increased FDW CI and FDW ΔP. FDW CI/FCW CI and FDW ΔP/FCW ΔP are surrogate ratios indexing the ventricular relaxation to the systolic force.

Milrinone has been reported to improve ventricular diastolic relaxation and promote lusitropy (41). This has been demonstrated in vitro in a single ventricular myocyte (47) and also in vivo in dogs (10). Fredholm et al (48) demonstrated improved diastolic function using strain imaging in patients after aortic valve surgery. Similarly, echocardiographic assessment demonstrated improved peak filling rate in adult patients after coronary artery bypass grafting (49).

This understanding, however, is far from universal. Dewitt et al (8) demonstrated a lack of improvement in diastolic function with milrinone when preload and afterload were maintained constant. In lipopolysaccharide-treated rabbits, milrinone did not improve ventricular diastolic function (50). Also, it did not add to the natural recovery of the post-CPB LV diastolic dysfunction in adult patients (51, 52). These findings are consistent with our study where milrinone produced no change in the ventricular diastolic function as evidenced by the lack of change in FDW-related variables.

The lack of improvement in systolic or diastolic ventricular function is interesting and may be due to the fact that a certain fraction of patients in our cohort may have been in the acute postoperative phase, and the findings may have been confounded by the dynamic nature of LCOS. However, the median time to starting milrinone was 71 hours after CPB, which makes this unlikely.

Our study has important limitations. Due to inherent difficulty with postoperative imaging after sternotomy in children after cardiac surgery, a certain amount of data, especially from transthoracic echocardiography, were of inadequate quality for analysis. However, WIA data were not affected as the doppler images were obtained from the common carotid artery in the neck. Although the study sample size is modest, it represents the typical spectrum of children after congenital heart disease surgery who receive milrinone. The pre- and postdesign accounts for each patient to serve as their own control limiting the confounding factors. Despite the sample size limitations, WIA was sensitive enough to detect significant characteristic changes, findings that provide the basis for ongoing and further investigation.

## CONCLUSIONS

We found that milrinone acted as a vasodilator but did not improve contractility or relaxation of the left ventricle as assessed by WIA. Our study suggests that the effects of milrinone are predominantly due to a reduction in afterload, with no major effect on contractility or relaxation properties of the myocardium. However, larger clinical studies are required to confirm our findings. We were also able to demonstrate that WIA could be safely performed by the bedside to yield valuable information regarding ventriculo-vascular interactions in critically ill children following cardiac surgery. WIA is a promising research and clinical imaging tool in cardiac ICU.

Dr. Mynard's institution received funding from National Health and Medical Research Council of Australia and National Heart Foundation of Australia. The remaining authors have disclosed that they do not have any potential conflicts of interest.

For information regarding this article, E-mail: Sarfaraz.Rahiman@health.qld.gov.au

This study was conducted in the PICU, Royal Children's Hospital, Melbourne.

## REFERENCES

1. Hoffman TM, Wernovsky G, Atz AM, et al: Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003; 107:996–1002
2. Barton P, Garcia J, Kouatli A, et al: Hemodynamic effects of i.v. milrinone lactate in pediatric patients with septic shock. A prospective, double-blinded, randomized, placebo-controlled, interventional study. *Chest* 1996; 109:1302–1312
3. Chang AC, Atz AM, Wernovsky G, et al: Milrinone: Systemic and pulmonary hemodynamic effects in neonates after cardiac surgery. *Crit Care Med* 1995; 23:1907–1914
4. Baim DS, McDowell AV, Cherniles J, et al: Evaluation of a new bipyridine inotropic agent–milrinone–in patients with severe congestive heart failure. *N Engl J Med* 1983; 309:748–756
5. Monrad ES, Baim DS, Smith HS, et al: Milrinone, dobutamine, and nitroprusside: Comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation* 1986; 73(3 Pt 2):Iii168–174
6. Duggal B, Pratap U, Slavik Z, et al: Milrinone and low cardiac output following cardiac surgery in infants: Is there a direct myocardial effect? *Pediatr Cardiol* 2005; 26:642–645
7. Stocker CF, Shekerdemian LS, Nørgaard MA, et al: Mechanisms of a reduced cardiac output and the effects of milrinone and levosimendan in a model of infant cardiopulmonary bypass. *Crit Care Med* 2007; 35:252–259
8. DeWitt ES, Black KJ, Thiagarajan RR, et al: Effects of commonly used inotropes on myocardial function and oxygen consumption under constant ventricular loading conditions. *J Appl Physiol (1985)* 2016; 121:7–14
9. Jaski BE, Fifer MA, Wright RF, et al: Positive inotropic and vasodilator actions of milrinone in patients with severe congestive heart failure. Dose-response relationships and comparison to nitroprusside. *J Clin Invest* 1985; 75:643–649
10. Yano M, Kohno M, Ohkusa T, et al: Effect of milrinone on left ventricular relaxation and Ca(2+) uptake function of cardiac sarcoplasmic reticulum. *Am J Physiol Heart Circ Physiol* 2000; 279:H1898–H1905
11. Japp AG, Moir S, Mottram PM: Echocardiographic quantification of left ventricular systolic function. *Heart Lung Circ* 2015; 24:532–535
12. Boudoulas KD, Triposkiadis F, Boudoulas H: Evaluation of left ventricular performance: Is there a gold standard? *Cardiology* 2018; 140:257–261

13. Bos GCVD, Elzinga G, Westerhof N, et al: Problems in the use of indices of myocardial contractility. *Cardiovasc Res* 1973; 7:834–848
14. Hughes AD, Parker KH: Forward and backward waves in the arterial system: Impedance or wave intensity analysis? *Med Biol Eng Comput* 2009; 47:207–210
15. Li Y, Guo L: Clinical value of carotid wave intensity analysis for differentiating nonobstructive hypertrophic cardiomyopathy from left ventricular hypertrophy secondary to systemic hypertension. *J Clin Ultrasound* 2013; 41:151–157
16. Sugawara M, Niki K, Ohte N, et al: Clinical usefulness of wave intensity analysis. *Med Biol Eng Comput* 2009; 47:197–206
17. Hughes AD, Parker KH, Davies JE: Waves in arteries: A review of wave intensity analysis in the systemic and coronary circulations. *Artery Res* 2008; 2:51–59
18. Shann F: Paediatric Intensive Care Guidelines. 4th Edition. Royal Children's Hospital, Melbourne, VIC, Australia, 2017
19. Gerhard-Herman M, Gardin JM, Jaff M, et al; American Society of Echocardiography; Society for Vascular Medicine and Biology: Guidelines for noninvasive vascular laboratory testing: A report from the American Society of Echocardiography and the Society for Vascular Medicine and Biology. *Vasc Med* 2006; 11:183–200
20. Savitzky A, Golay MJE: Smoothing and differentiation of data by simplified least squares procedures. *Anal Chem* 1964; 36:1627–1639
21. Watanabe H, Kawai M, Sibata T, et al: Noninvasive measurement of aortic pressure waveform by ultrasound. *Heart Vessels* 1998; 13: 79–86
22. Harada A, Okada T, Niki K, et al: On-line noninvasive one-point measurements of pulse wave velocity. *Heart Vessels* 2002; 17:61–68
23. Kowalski R, Beare R, Willemet M, et al: Robust and practical noninvasive estimation of local arterial wave speed and mean blood velocity waveforms. *Physiol Meas* 2017; 38:2081–2099
24. Davies JE, Whinnett ZI, Francis DP, et al: Use of simultaneous pressure and velocity measurements to estimate arterial wave speed at a single site in humans. *Am J Physiol Heart Circ Physiol* 2006; 290:H878–H885
25. Jones CJ, Sugawara M, Kondoh Y, et al: Compression and expansion wavefront travel in canine ascending aortic flow: Wave intensity analysis. *Heart Vessels* 2002; 16:91–98
26. Penny DJ, Mynard JP, Smolich JJ: Aortic wave intensity analysis of ventricular-vascular interaction during incremental dobutamine infusion in adult sheep. *Am J Physiol Heart Circ Physiol* 2008; 294:H481–H489
27. Parker KH: An introduction to wave intensity analysis. *Med Biol Eng Comput* 2009; 47:175–188
28. Mynard JP, Smolich JJ: Wave potential and the one-dimensional windkessel as a wave-based paradigm of diastolic arterial hemodynamics. *Am J Physiol Heart Circ Physiol* 2014; 307:H307–H318
29. Laurent S, Cockcroft J, Van Bortel L, et al; European Network for Noninvasive Investigation of Large Arteries: Expert consensus document on arterial stiffness: Methodological issues and clinical applications. *Eur Heart J* 2006; 27:2588–2605
30. Kolyva C, Khir A: Wave intensity analysis in the great arteries–What has been learnt during the last 25 years? Part 1. *International Cardiovascular Forum* 2013;1:68–73
31. Saiki H, Kurishima C, Masutani S, et al: Cerebral circulation in patients with Fontan circulation: Assessment by carotid arterial wave intensity and stiffness. *Ann Thorac Surg* 2014; 97:1394–1399
32. Bleasdale RA, Mumford CE, Campbell RI, et al: Wave intensity analysis from the common carotid artery: A new noninvasive index of cerebral vasomotor tone. *Heart Vessels* 2003; 18:202–206
33. Kowalski R, Lee MGY, Doyle LW, et al: Reduced aortic distensibility is associated with higher aorto-carotid wave transmission and central aortic systolic pressure in young adults after coarctation repair. *J Am Heart Assoc* 2019; 8:e011411
34. Parragh S, Hametner B, Bachler M, et al: Non-invasive wave reflection quantification in patients with reduced ejection fraction. *Physiol Meas* 2015; 36:179–190
35. Vriz O, Zito C, di Bello V, et al: Non-invasive one-point carotid wave intensity in a large group of healthy subjects: A ventricular-arterial coupling parameter. *Heart Vessels* 2016; 31:360–369
36. Fujimoto S, Mizuno R, Saito Y, et al: Clinical application of wave intensity for the treatment of essential hypertension. *Heart Vessels* 2004; 19:19–22
37. Fok H, Guilcher A, Brett S, et al: Dominance of the forward compression wave in determining pulsatile components of blood pressure: Similarities between inotropic stimulation and essential hypertension. *Hypertension* 2014; 64:1116–1123
38. Royse CF, Royse AG, Rohrlach R, et al: The cardiovascular effects of adrenaline, dobutamine and milrinone in rabbits using pressure-volume loops and guinea pig isolated atrial tissue. *Anaesth Intensive Care* 2007; 35:180–188
39. Liu JJ, Doolan LA, Xie B, et al: Direct vasodilator effect of milrinone, an inotropic drug, on arterial coronary bypass grafts. FANZCA. *J Thorac Cardiovasc Surg* 1997; 113:108–113
40. Baruch L, Patacsil P, Hameed A, et al: Pharmacodynamic effects of milrinone with and without a bolus loading infusion. *Am Heart J* 2001; 141:266–273
41. Axelsson B, Häggmark S, Svenmarker S, et al: Effects of combined milrinone and levosimendan treatment on systolic and diastolic function during postischemic myocardial dysfunction in a porcine model. *J Cardiovasc Pharmacol Ther* 2016; 21:495–503
42. Nakayama T, Nishijima Y, Miyamoto M, et al: Effects of 4 classes of cardiovascular drugs on ventricular function in dogs with mitral regurgitation. *J Vet Intern Med* 2007; 21:445–450
43. Osuga T, Nakamura K, Morita T, et al: Effects of various cardiovascular drugs on indices obtained with two-dimensional speckle tracking echocardiography of the left atrium and time-left atrial area curve analysis in healthy dogs. *Am J Vet Res* 2015; 76:702–709
44. Yano M, Kohno M, Ohkusa T, et al: Effect of milrinone on left ventricular relaxation and Ca2+ uptake function of cardiac sarcoplasmic reticulum. *Am J Physiol Heart Circ Physiol* 2000; 279:H1898–H1905
45. Artman M, Kithas PA, Wike JS, et al: Inotropic responses change during postnatal maturation in rabbit. *Am J Physiol* 1988; 255:H335–H342
46. Hyldebrandt JA, Larsen SH, Schmidt MR, et al: Age-dependent effects of milrinone and levosimendan on ventricular function and haemodynamics in newborn and mature pigs. *Cardiol Young* 2011; 21:518–527
47. Farah AE, Canniff PC, Bentley R, et al: Effect of milrinone (Corotrope) on the contractility of isolated dog ventricular muscle. *J Cardiovasc Pharmacol* 1987; 10:607–615
48. Fredholm M, Jörgensen K, Houltz E, et al: Inotropic and lusitropic effects of levosimendan and milrinone assessed by strain echocardiography-A randomised trial. *Acta Anaesthesiol Scand* 2018; 62:1246–1254
49. Axelsson B, Arbeus M, Magnuson A, et al: Milrinone improves diastolic function in coronary artery bypass surgery as assessed by acoustic quantification and peak filling rate: A prospective randomized study. *J Cardiothorac Vasc Anesth* 2010; 24:244–249
50. Barraud D, Faivre V, Damy T, et al: Levosimendan restores both systolic and diastolic cardiac performance in lipopolysaccharide-treated rabbits: Comparison with dobutamine and milrinone. *Crit Care Med* 2007; 35:1376–1382
51. Lobato EB, Willert JL, Looke TD, et al: Effects of milrinone versus epinephrine on left ventricular relaxation after cardiopulmonary bypass following myocardial revascularization: Assessment by color m-mode and tissue Doppler. *J Cardiothorac Vasc Anesth* 2005; 19:334–339
52. Couture P, Denault AY, Pellerin M, et al: Milrinone enhances systolic, but not diastolic function during coronary artery bypass grafting surgery. *Can J Anaesth* 2007; 54:509–522