Treatment of Subarachnoid Hemorrhage-associated Delayed Cerebral Ischemia With Milrinone: A Review and Proposal

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Abstract: Delayed cerebral ischemia (DCI) following aneurysmal subarachnoid hemorrhage continues to be associated with high levels of morbidity and mortality. This complication had long been thought to occur secondary to severe cerebral vasospasm, but expert opinion now favors a multifactorial etiology, opening the possibility of new therapies. To date, no definitive treatment option for DCI has been recommended as standard of care, highlighting a need for further research into potential therapies. Milrinone has been identified as a promising therapeutic agent for DCI, possessing a mechanism of action for the reversal of cerebral vasospasm as well as potentially anti-inflammatory effects to treat the underlying etiology of DCI. Intra-arterial and intravenous administration of milrinone has been evaluated for the treatment of DCI in single-center case series and cohorts and appears safe and associated with improved clinical outcomes. Recent results have also brought attention to the potential out-of-hospitalization benefits of early, more aggressive dosing and titration of milrinone. Limitations exist within the available data, however, and questions remain about the generalizability of results across a broader spectrum of patients suffering from DCI. The development of a standardized protocol for milrinone use in DCI, specifically addressing areas requiring further clarification, is needed. Data generated from a standardized protocol may provide the impetus for a multicenter, randomized control trial. We review the current literature on milrinone for the treatment of DCI and propose a preliminary standardized protocol for further evaluation of both safety and efficacy of milrinone.

Key Words: aneurysmal subarachnoid hemorrhage, delayed cerebral ischemia, milrinone, outcome

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The incidence of aneurysmal subarachnoid hemorrhage (aSAH) is between 9.7 and 14.5 per 100,000 hospitalized adults in the United States and between 2 and 16.5 per 100,000 hospitalized adults globally. Early securement of the ruptured aneurysm is paramount and has been demonstrated to improve clinical outcomes through a reduction in rebleeding rates. Despite early aneurysm securement, aSAH patients may still face devastating neurological decline secondary to rebleeding, hydrocephalus, seizures, infections, cerebral vasospasm, and delayed cerebral ischemia (DCI).

DCI occurs in approximately one-third of patients after aneurysm rupture and carries significant risks for mortality and morbidity. In patients who experience DCI, ~15% to 20% will die or develop an ischemic stroke. Cerebral infarct development confers poor long-term functional outcomes. DCI typically occurs between 4 and 14 days after the initial bleed, with symptoms consisting of neurological changes including cognitive problems, decreased consciousness or focal deficits. The diagnosis of DCI is made after exclusion of other clinical, imaging, and/or laboratory abnormalities that might explain the new neurological deterioration. The overlapping time course of presentation of cerebral vasospasm and DCI has led to DCI being considered a complication of cerebral vasospasm. However, recent evidence suggests that the cause of aSAH-related DCI is likely multifactorial, related to vascular and neural changes including inflammation,
seizures, and metabolic/systemic dysfunction.\textsuperscript{8,9} Cerebral vasospasm likely contributes to the development of DCI after aSAH, although patients may develop both cerebral vasospasm and DCI together or independently. Acknowledging the presence of cerebral vasospasm as a component, but not the sole etiology, of DCI, while expanding research into therapeutics that address the multifactorial etiology of DCI, may be beneficial in improving clinical outcomes.

The high morbidity and mortality rates associated with aSAH-related DCI have led to exploration into many strategies targeting prevention or treatment of DCI with varying degrees of success. Dihydropyridine calcium channel blockers have been studied as prophylactic agents and for treatment of cerebral vasospasm/DCI after aSAH. Oral nimodipine, with a presumed cellular neuroprotective mechanism independent of its vasodilatory effect, is recommended in all patients with aSAH to improve neurological outcomes, though it does not appear to impact cerebral vasospasm/DCI.\textsuperscript{3,10,11} Intra-arterial (IA) vasodilators, such as nicardipine, verapamil and papaverine, and induction of systemic hypertension, have previously been used to treat DCI. However, evidence of benefit has been inconclusive and these interventions are associated with significant adverse events.\textsuperscript{3,12–14} The paucity of data demonstrating efficacy for IA therapy, induced hypertension, and various other interventions to effectively prevent or reverse DCI after aSAH has created a need to evaluate new therapeutic options.

Milrinone has been identified as a promising medication to improve outcomes in aSAH patients who experience DCI. It has been evaluated in small case series and single-center, retrospective cohort studies that have investigated two distinct treatment approaches: the combination of IA and intravenous (IV) therapy, or IV monotherapy. The purpose of this narrative review is to evaluate the use of milrinone for the treatment of aSAH with DCI. While cardiac output augmentation and afterload reduction support the benefit of milrinone use in cardiac patient populations, the mechanism of potential benefit for treating DCI after aSAH patients remains unclear. Reduction in vascular tone by milrinone may contribute directly to lessening severity of cerebral vasospasm.\textsuperscript{15,16} Increasing cardiac

\textbf{METHODS}

A systemic search was conducted in MEDLINE (1945 through May 2020) and EMBASE (1974 through May 2020) for human, English-language studies evaluating the use of milrinone for the treatment of DCI after aSAH (Fig. 1). The following terms were used in the search: \textit{milrinone} and \textit{aneurysmal subarachnoid hemorrhage}. Key articles were cross-referenced for additional studies. Studies were included in this review if patients diagnosed with aSAH and successful source of bleeding had undergone subsequent treatment with milrinone for DCI or cerebral vasospasm with neurological changes. Studies were excluded under the following criteria: (1) a nonclinical primary endpoint; (2) milrinone was used for an indication other than DCI or cerebral vasospasm with neurological changes; (3) an additional experimental intervention was made beyond milrinone; (4) the route of milrinone administration was not IA or IV; (5) single patient case reports, and/or; (6) review articles. The first author (T.B.) performed the literature search and initial screening of articles for inclusion based on titles and abstracts. All included and excluded articles were reviewed with any discrepancies resolved after discussion with all co-authors.

\textbf{PHARMACOLOGY OF MILRINONE}

Milrinone antagonizes the phosphodiesterase III enzyme that hydrolyzes cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). The subsequent increase in cAMP leads to an increase in inotropy and lusitropy, while the increase in cGMP leads to smooth muscle relaxation in both arterial and venous vasculatures. These changes result in increased cardiac output and vasodilation. Given these properties, milrinone has been extensively used for the treatment of advanced decompensated heart failure and cardiogenic shock. The IV dose of milrinone for cardiac indications typically ranges from 0.1 to 0.75 µg/kg/min, which is lower than the doses used in the studies investigating milrinone in the management of cerebral vasospasm and DCI reviewed below.

While cardiac output augmentation and afterload reduction support the benefit of milrinone use in cardiac patient populations, the mechanism of potential benefit for treating DCI after aSAH patients remains unclear. Reduction in vascular tone by milrinone may contribute directly to lessening severity of cerebral vasospasm.\textsuperscript{15,16} Increasing cardiac
output without the vasoconstriction caused by vasopressors may be an additional advantage. An improvement in cerebral microcirculation because of the increase in cGMP may also be beneficial. Finally, the reduction in cAMP results in reduced cytokine production, conferring potentially beneficial anti-inflammatory effects.\textsuperscript{17–21} Importantly, milrinone has no known effect on reducing other neural changes in aSAH, such as seizures and/or metabolic/systemic changes. Further research is needed into other therapeutics to address potential causes of DCI.

**EVIDENCE FOR THE USE OF MILRINONE IN THE TREATMENT OF DCI**

Six studies evaluating the use of milrinone for the treatment of DCI after aSAH were identified for inclusion in this review (Fig. 1).\textsuperscript{22–27} Three assessed initial IA administration of milrinone followed by IV administration,\textsuperscript{22–24} 2 the IV administration of milrinone alone,\textsuperscript{25,26} and 2 the escalation of milrinone therapy for refractory DCI.\textsuperscript{27} The findings of these studies are summarized in the subsequent sections, followed by a discussion of the overall efficacy and safety of milrinone in the treatment of DCI.

### IA Milrinone

The 3 case series describing the clinical experiences of IA milrinone for the treatment of DCI are summarized in Table 1. The infusion of milrinone directly into affected cerebral vessel(s) for the treatment of cerebral vasospasm or DCI was first described in 2001.\textsuperscript{22} In this first report of 7 aSAH patients with symptomatic angiographic cerebral vasospasm, IA milrinone led to satisfactory vasodilation in all patients with significant increases in middle cerebral artery diameter in both M1 and M2 segments. Neurological symptoms improved gradually for a few hours after IA infusion in 7 of 12 milrinone treatments, although no long-term clinical outcomes were reported. There were no significant changes in mean arterial pressure (MAP) or heart rate during IA milrinone infusion in this study. A subsequent case series of 15 treatments in 14 patients also suggested benefit from IA milrinone infusion, with significant angiographic improvement reported.\textsuperscript{23} Notably, 9 of the 14 patients in this series had favorable outcomes (modified Rankin score [mRS] \(\leq 3\)) at discharge, and only 1 patient died. Another case series of 22 patients also reported that IA milrinone was a safe and effective treatment for aSAH-related cerebral vasospasm; milrinone was associated with a significant increase in vessel diameter.\textsuperscript{24} Two patients required norepinephrine infusion for hypotension and 8 patients required mechanical angioplasty. Nine of 18 known patients were able to resume all previous daily activities, while 2 patients died before discharge.

In summary, in 3 small uncontrolled case series, IA administration of milrinone increased angiographic vessel diameter and only 2 of 44 patients required hemodynamic support.\textsuperscript{22–24}

### IV Milrinone

The 2 case series describing the clinical experiences of IV milrinone for the treatment of DCI are summarized in Table 2. A group from the Montreal Neurological Institute...
<table>
<thead>
<tr>
<th>References</th>
<th>Number of Patients</th>
<th>Milrinone Dosing Strategy</th>
<th>Reversal of Cerebral Vasospasm</th>
<th>Clinical Outcomes</th>
<th>Recurrence of Symptoms</th>
<th>Adverse Events/Safety Data</th>
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<tr>
<td>Lannes et al²⁵</td>
<td>88</td>
<td>IV: 0.1-0.2 bolus of milrinone; start infusion at 0.75 µg/kg/min; titrate to maximum of 1.25 µg/kg/min if no improvement after 30 minutes. Rescue therapy: additional milrinone boluses and/or angioplasty permitted in patients with inadequate clinical response.</td>
<td>87/88 (99%)*</td>
<td>Mortality: 5/88 (5.7%) patients</td>
<td>1/88 (1%)</td>
<td>Need for angioplasty: 0/88 (0%) patients</td>
</tr>
<tr>
<td>Crespy et al²⁶</td>
<td>IA+IV: 24</td>
<td>IA+IV: 5 mg per region/treatment (maximum 24 mg per patient); 1 µg/kg/min IV for up to 2 wk hours in neurologic status without escalation of IV milrinone.</td>
<td>IA+IV: 37/52 (71%) vasospastic regions†</td>
<td>Mortality (IA+IV; IV): 4/24 (17%) patients; 2/77 (3%) patients</td>
<td>IA+IV: 4/24 (17%) required rescue procedures</td>
<td>Escalation of vasopressor dose (IA+IV; IV): 12/24 (50%); 3/77 (4%) patients</td>
</tr>
<tr>
<td></td>
<td>IV: 77</td>
<td>IV: initiated at 0.5-1 µg/kg/min per day based on patient factors; boluses of 8 mg per day in cases of DCI; maintained for at least 7 d.</td>
<td>IV: 125/194 (64%) vasospastic regions†</td>
<td>mRS ≤ 2 (IA+IV; IV): 16/24 (67%) patients; 59/77 (77%) patients</td>
<td>15/77 (18%) required rescue procedures</td>
<td>Hemodynamic instability (IA+IV; IV): 1/24 (4%); 2/77 (3%) patients</td>
</tr>
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*Clinical response.
†Angiographic reversal of vasospasm.
IA indicates intra-arterial; IV, intravenous; mRS, modified Rankin score.

### Milrinone for the Treatment of Refractory DCI

Although the above mentioned study²⁶ found that IV milrinone was effective for the treatment of DCI, it was not able to identify which patients would be more likely to benefit from milrinone therapy without IA therapy. A retrospective comparison of IA+IV milrinone versus IV milrinone found no significant differences in clinical outcomes for patients with poor grade aSAH. Patients who were treated with IA therapy had a similar efficacy between the two treatment regimes. Reversal of vasospasm-related symptoms and clinical outcomes did not differ between the groups in the IV arm. There was also no significant difference in the rate of vasospasm-related symptoms and clinical outcomes between the groups in the IA+IV arm. The study concluded that milrinone was effective for the treatment of DCI, but further research is needed to identify which patients would be more likely to benefit from this treatment.

**Note:** 75% of patients had Hunt and Hess scores of 1 to 3 at baseline.
decision-making process. Among patients who developed cerebral vasospasm/DCI, 19% required rescue therapy and 76% of those patients demonstrated clinical improvement within 24 hours. Two multivariable analyses of patient characteristics associated with response to either IV therapy or IV+IA rescue therapy were performed. Higher WFNS grade, mild radiographic vasospasm, and moderate/severe radiographic vasospasm were independent predictors of IV therapy, while only moderate/severe vasospasm was predictive of the need for rescue therapy. Although these findings provide potential insights into characteristics that can be used to identify which aSAH patients are most likely to benefit from milrinone, additional confirmatory studies are required.

This study also reported imaging and clinical outcomes.27 New cerebral infarction developed in 40% of the 277 patients with neuroimaging available; 21% of all new infarcts were attributed to cerebral vasospasm, and only 2 additional cerebral vasospasm-related infarcts were identified postdischarge. The incidence of cerebral vasospasm-related infarction was significantly higher in both the IV milrinone and IV+IA rescue therapy groups than in patients who did not demonstrate any clinical signs of DCI and thus did not receive milrinone. The incidence of noncerebral vasospasm-related infarction was not significantly different among the 3 groups. Despite the higher incidence of cerebral vasospasm-related infarction, functional outcomes did not significantly differ across the 322 patients in the 3 treatment groups. Favorable functional outcomes (mRS ≤ 2) were observed in 65% of all patients at a median of 4 months after the initial bleeding event. This lack of difference in clinical outcomes potentially highlights an additional benefit for milrinone in DCI, as good clinical outcomes may be related to more than prevention of cerebral vasospasm-related infarction.

This study also expanded upon the specifics of IV milrinone dosing.27 The median (interquartile range [IQR]) IV dose of milrinone before rescue therapy was 1.25 µg/kg/min (IQR: 1.0 to 1.5 µg/kg/min), and increased to 1.75 µg/kg/min (IQR: 1.5 to 2.0 µg/kg/min) following rescue therapy; only 2 patients required the maximum dose of 2.5 µg/kg/min following rescue therapy. Maximum doses of IV milrinone infusion were based on the severity of radiographic vasospasm; the average dose of milrinone was 1.07 ± 0.47 µg/kg/min in patients with mild radiographic vasospasm, 1.08 ± 0.40 µg/kg/min in patients with moderate severity vasospasm, and 1.35 ± 0.54 µg/kg/min in patients with severe radiologic vasospasm; average doses were significantly different across the 3 groups (P = 0.026). These findings could provide potential guidance for infusion ranges based on radiographic findings, though confirmation across multiple patient populations would be needed. In-hospital mortality because of cerebral infarction occurred in 8 patients in the IV monotherapy arm with 0 deaths in those who also received rescue therapy; these findings suggest that earlier aggressive milrinone therapy may be associated with additional benefits. Of note, this apparent benefit may not have been solely because of the addition of IA milrinone as patients in the rescue therapy group also received higher doses of IV milrinone per protocol following IA therapy.

In terms of safety, adverse events were rarely observed in both milrinone treatment regimens (IA+IV and IV alone) in this study.27 No differences were observed among groups in the development of new or worsening arrhythmias, hypokalemia, or pulmonary edema. Hypotension, defined as a > 25% decrease in systolic blood pressure within 1 day after starting milrinone therapy and requiring vasopressor therapy for longer than 1 day, was reported in 15% of patients who received milrinone. In an effort to re-establish baseline blood pressure, vasopressors were additionally used in patients experiencing a 20% MAP decrease from baseline, resulting in 40% of patients receiving vasopressors. Transient myocardial ischemia, requiring holding or decreasing of milrinone infusion rate, developed in 2 patients. One of the 2 patients who developed transient myocardial ischemia had known aortic stenosis. Nineteen percent of patients who received IV milrinone reported a history of cardiac disease, however, no other specifics were provided.

While this study provides greater insights not only into the use of IV milrinone but also IA rescue therapy, it is worth noting that neuroimaging data were missing in 14% of patients at the time of discharge and in 35% during the follow-up period; this weakens the results dependent on these data points. Moreover, factors associated with response and/or need for IV and IA rescue therapy were observed during clinical practice and should not be viewed as causal relationships. Adequate evidence to guide therapy with milrinone will require more rigorous study.

Efficacy of Milrinone for the Treatment of DCI
On the basis of the available data, it appears that IV milrinone and IA+IV milrinone might be efficacious in the treatment of DCI.22-27 To add perspective, an analysis of aSAH patients admitted to hospital between 2001 and 2013 found that 63% had an excellent outcome (mRS ≤ 1) at 12 months; however, only 29% of patients with an excellent outcome experienced DCI.28 In contrast, the percentage of DCI patients who are able to achieve a functional status of mRS ≤ 2 has been reported to range between 65% and 77% when treated with either IV or IA+IV milrinone.25-27 Notably, this finding is consistent across patients regardless of WFNS grade, with those with more severe grades potentially responding to more aggressive therapy. Further, the incidence of new cerebral infarction attributed to cerebral vasospasm was only 21% in the most recent study from the Montreal Neurological Institute,27 compared with a historical reported incidence of 50% of patients with DCI.3 Milrinone efficacy is further supported by similar functional outcomes being observed independent of the incidence of cerebral vasospasm-related infarction.21 However, existing data are derived from single-center case series and not randomized controlled trials, so definitive clinical benefits remain unclear.

Safety of Milrinone for the Treatment of DCI
The safety of both IV and IA+IV milrinone for the treatment of aSAH-related DCI appears to be supported across all case series.22-27 The most consistently reported adverse event was hypotension, which appeared to increase with dose escalation of IV therapy. Use of vasopressor therapy to reverse milrinone-induced hypotension appears to be safe; no
Complications attributed to the addition of vasopressors were reported across all case series. Arrhythmias were infrequent, occurring in 0% to 7% of patients who received milrinone with no statistically significant differences observed regardless of receipt of milrinone. In addition, no significant episodes of hypokalemia or hypomagnesemia attributed to milrinone were reported. The use of IV milrinone at much higher doses than standard cardiovascular dosing is concerning for the potential development of myocardial ischemia. However, the incidence of myocardial ischemia appears to be low, occurring in only 2 of 555 patients across all case series. Nonetheless, patients with extensive cardiac risk factors were not well represented in these studies, so the potential risks of higher infusion rates in this population are unknown. Significant cardiovascular history should therefore warrant caution, especially if approaching higher doses of milrinone infusion; different underlying diagnoses may carry varying risks of complications. Finally, the available case series also do not address potential adverse effects related to decreased clearance of milrinone secondary to reduced renal function. Thus, until further evidence is available, aggressive milrinone therapy for DCI should be used cautiously in patients with severe renal dysfunction.

**PROPOSED PROTOCOL FOR MILRINONE USE IN DCI**

While further evaluation is necessary to assess the reproducibility of the single-center case series and cohort studies discussed above, the following protocol for the use of milrinone for the treatment of DCI has been developed by the authors of this review (Fig. 2). In this protocol, the initial bolus of crystalloids, initial bolus dose and rate of milrinone infusion, subsequent bolus dose and timing intervals, definition of cerebral vasospasm severity, timing for invasive intervention, and duration and weaning of milrinone infusion are based upon the Montreal Neurological Institute experiences. The subsequent dose titration of milrinone infusion,

![Flowchart diagram](image-url)
target dose of the infusion based on cerebral vasospasm severity, IA intervention dosing, and maximum dose of milrinone infusion in the protocol are based on the expert opinion of the author group.

We recommend that IV milrinone monotherapy should be initiated in patients who meet the following criteria: (1) confirmed aSAH and secured aneurysm; (2) new symptoms consistent with DCI; (3) no severe cardiac compromise or other significant hemodynamic instability; and (4) baseline creatinine clearance > 30 mL/min. The diagnosis of DCI is defined as a new, sustained focal neurological deficit lasting at least 1 hour that is not apparent immediately after aneurysm occlusion and not attributable to any other clinical event or diagnosis through imaging or laboratory measurements.6,7

The definition for a new sustained focal neurological deficit is: (1) new changes in level of consciousness or orientation on at least 2 serial assessments, decline of a significant magnitude in Glasgow coma scale in the total or subscore (≥ 2 points), cranial nerve palsy, pronator drift, or focal motor deficit; and (2) a rapidly occurring deficit (within a 4-h window).6,7,27

Milrinone therapy should not replace or lead to the removal of any element of established medical care for DCI.

Cranial imaging (computed tomography angiography, digital subtraction angiography, or transcranial Doppler) evaluating for cerebral vasospasm should be obtained and determination of severity documented. Radiographic classification of cerebral vasospasm is based on the degree of vessel luminal narrowing using computed tomography angiography or digital subtraction angiography: mild vasospasm (< 25%), moderate vasospasm (25% to 50%), or severe vasospasm (> 50%).27

Transcranial Doppler-defined severity of vasospasm is based on mean middle cerebral artery flow velocity and middle cerebral artery/internal carotid artery mean flow velocity ratio: mild (> 120 cm/s and 3 to 4, respectively), moderate (> 120 cm/s and 5 to 6, respectively), or severe (> 180 cm/s and > 6, respectively).27

The recommended target milrinone dose ranges are: 0.75 to 1.25 µg/kg/min for mild vasospasm, 1.0 to 1.5 µg/kg/min for moderate vasospasm, and 1.0 to 2.0 µg/kg/min for severe vasospasm. Nimodipine therapy should be continued with milrinone initiation and throughout therapy; however, doses of nimodipine may be reduced or held in cases of hemodynamic instability.

If hemodynamic instability from baseline occurs (ie, decrease in MAP ≥ 20% or MAP < 75 mm Hg), a bolus of ≥ 500 mL crystalloid should be administered and vasopressors initiated if the patient remains unstable despite adequate fluid resuscitation. If hemodynamic instability persists despite use of vasopressors, milrinone infusion should be reduced by 0.25 µg/kg/min decrements every 1 to 2 hours until hemodynamic stability is re-established. The IV milrinone infusion should be maintained until 72 hours after the last symptomatic episode, and thereafter be weaned in 0.25 µg/kg/min decrements every 24 hours. If symptoms return during the weaning process, a 50 µg/kg IV bolus of milrinone can be administered and the infusion rate should be returned to the last dose at which the patient was asymptomatic. All future weaning attempts should then be held for a period of 24 hours.

Patients should have serial electrocardiograms based on clinical judgment and be placed on continuous cardiac monitors to be assessed hourly and after each dose escalation. Regular electrolyte monitoring should occur while the patient is receiving milrinone. Cardiac troponins should also be assessed and trended in cases of potential cardiac ischemia.

Patients should undergo an adequate trial of IV milrinone, as described above and in Figure 2, before the pursuit of intravascular intervention. In cases of acute worsening of the clinical condition despite aggressive titration of IV therapy, or inability to tolerate IV milrinone, invasive intravascular treatment may be pursued at the managing clinician’s discretion.

When assessing the efficacy of milrinone therapy, primary clinical outcomes may include need for rescue therapy because of new or worsening neurological symptoms, incidence of cerebral vasospasm-related cerebral infarcts within 6 weeks of aSAH, and good functional outcomes (mRS ≤ 2) at 1, 3, and 12 months after the initial bleed in comparison to standard medical therapy. Secondary clinical outcomes should include subgroup analyses of primary outcomes according to baseline WFNS grade (I to III compared with IV to V) and severity of vasospasm. The primary safety outcome should include the rate of adverse events requiring discontinuation of therapy, and secondary safety outcomes the incidence of hypotension, need for vasopressors, and incidence of arrhythmias, myocardial ischemia, and electrolyte abnormalities.

CONCLUSION
The available, albeit limited, evidence suggests that IA and IV milrinone are safe and effective treatments for DCI and associated with improved long-term functional outcomes. However, studies to date are limited to retrospective case series and single-center cohorts. Adequate evidence for use of milrinone in the treatment of DCI will necessarily require larger, multicenter clinical trials. Therefore, we hope that use of the preliminary protocol proposed in this review will facilitate further evaluation into the safety and efficacy of milrinone for treating DCI after aSAH.

REFERENCES


