How Feasible is Extracorporeal Cardiopulmonary Resuscitation in a Medium Urban Population Centre?

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Abstract

Background

Patients suffering from out-of-hospital cardiac arrest (OHCA) experience poor survival and neurological outcomes, with rates remaining relatively unchanged despite advancements. Extracorporeal membrane oxygenation (ECMO), termed extracorporeal cardiopulmonary resuscitation (ECPR) in arrests, may offer improved outcomes. We developed local screening criteria for ECPR and then estimated the frequency of use by applying those criteria retrospectively to a cardiac arrest database. The purpose was to determine if an ECPR program is feasible in a medium urban population centre in Atlantic Canada.

Methods

A three-round modified Delphi survey, building upon data from a literature review, was conducted in collaboration with external experts. The resulting selection criteria for potential ECPR candidates were applied to a pre-existing local cardiac arrest database, supplemented by health records review, identifying potential candidates eligible for ECPR.

Results

Consensus inclusion criteria included witnessed cardiac arrest, age <70, refractory arrest, no-flow time <10min, total downtime <60min, and presumed cardiac or selected non-cardiac etiologies. Consensus exclusion criteria were an unwitnessed arrest, asystole, and select etiologies and comorbidities. Simplified criteria were developed to facilitate emergency medical services transport. Historically, 20.0% (95% CI 16.2-24.3%) of OHCA would be transported to the Emergency Department (ED), with 4.9% (95% CI 3.0% to 7.6%) qualifying for ECPR.

Conclusion

Despite conservative estimates based upon historically small numbers of select cardiac arrest patients meeting eligibility for transport and initiation of ECPR, a dedicated program may be feasible in our regional hospital setting. Patient care volumes suggest it would not be resource intensive yet would be sufficiently busy to maintain competency.

Categories: Cardiac/Thoracic/Vascular Surgery, Cardiology, Emergency Medicine

Keywords: cardiac arrest, resuscitation, extracorporeal membranous oxygenation

Introduction

Rates of neurologically intact survival from out of hospital cardiac arrest (OHCA) in adult patients are poor, with poor long-term outcomes [1]. The use of veno-arterial Extracorporeal Membrane Oxygenation (ECMO) in cardiac arrest, termed extracorporeal cardiopulmonary resuscitation (ECPR), may maintain vital organ perfusion, buying time for investigation and treatment of reversible causes of refractory arrest. ECPR is recognized internationally more recently as a potential tool to assist resuscitative efforts in the emergency department (ED) during cardiac arrest [2]. Observational data is suggestive that refractory OHCA treated with ECPR may lead to improved outcomes over those treated with conventional resuscitation, with survival rates as high as 48% [3].

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Tertiary healthcare facilities based in smaller and medium urban centres that provide interventional cardiac services face the uncertainty of how feasible and sustainable the introduction of an ECPR program is in their setting. We developed site-specific screening criteria for ECPR to predict the frequency of local ECPR events and applied those criteria retrospectively to a cardiac arrest database. Results were used to determine the feasibility of an ECPR program in our small metropolitan area within Atlantic Canada.

Materials And Methods

This study was undertaken using a sequential modified Delphi and database review methodology.

Determination of local ECPR selection criteria

Published patient selection criteria currently in use for ECPR were identified by literature review [4-9]. This list formed the basis of the modified Delphi survey, involving 13 local, regional, national, and international experts, including members representing pre-hospital care, emergency medicine, cardiology, intensive care medicine, cardiac surgery, anesthesia, and perfusion technology. The team liaised with established ECPR programs in Vancouver, British Columbia, and Sydney, New South Wales. Proposed transport and team activation inclusion and exclusion criteria were scored by a panel of 13 experts. A threshold of 60% consensus was required to progress to the next round, with a final consensus rate of over 80% required to close the survey. Additional local logistical factors were also reviewed. The final New Brunswick (NB) ECPR criteria were agreed upon following three rounds and additional review by an international expert.

Estimation of ECPR frequency

A cardiac arrest database review, supplemented by a health records review for missing data, was performed following the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) guidelines.

The NB-ECPR criteria were applied retrospectively to the complete database of adult patients presenting to an ED serving a medium urban population centre, in cardiac arrest, over a five-year period. Data were analyzed using standard parametric and non-parametric measures. Confidence intervals (CI) for proportions of 95% were calculated using the modified Wald method using GraphPad Software QuickCalcs, GraphPad Software, La Jolla California USA, <https://www.graphpad.com/quickcalcs/confInterval1/>.

Results

Modified Delphi survey

First-round responses achieved ≥87.5% consensus for the selection of exclusion criteria. Inclusion criteria had agreement ≥62.5%. Responses to the second round for inclusion criteria were unanimous at 100% with the exception of age parameters (<65 years versus <70 years). Age was proposed to be <70 years following ECPR team consultation. The final set of NB-ECPR criteria for transport to hospital, and for ECPR team activation (Table 1) achieved 100% consensus though subsequent expert review refined additional exclusion criterion based on experience (asystole). Inclusion criteria were witnessed cardiac arrest, age <70, refractory arrest, no-flow time <10 minutes, total downtime <60 minutes, and presumed cardiac or selected non-cardiac etiologies. Exclusion criteria were unwitnessed arrest, asystole, select etiologies, and comorbidities. Simplified criteria were developed to facilitate emergency medical services (EMS) transportation.

Criteria for Transport To Hospital		Criteria for ECPR Team Activation	
Inclusion Criteria	Exclusion Criteria	Inclusion Criteria	Exclusion Criteria
	X Unwitnessed Cardiac Arrest	✓ Witnessed Cardiac Arrest	X Unwitnessed Cardiac Arrest
	X Initial Rhythm Asystole	✓ Age <70 Years Old	X Asystole at Scene
✓ Witnessed Cardiac Arrest	X Suspected Etiology:	✓ No Flow Time <10min	X Suspected Etiology:
	-Uncontrolled Hemorrhage	✓ Total Downtime <60min	-Uncontrolled Hemorrhage
✓ Age <70 years old	-Irreversible Brain Damage	✓ Refractory Cardiac Arrest	-Irreversible Brain Damage
	-Trauma	✓ Suspected Etiology:	-Trauma
✓ No Flow Time <10 minutes	X Comorbidity:	-Cardiac	X Comorbidity:
	-Severe Disability Limiting ADLs	-Pulmonary Embolism	-Severe Disability Limiting ADLs
	-Standing DNR Order	-Drug OD / Poisoning	-Standing DNR Order
	-Undergoing Palliation	-Hypothermia	-Undergoing Palliation

TABLE 1: Final NB-ECPR criteria for transport to hospital and for ECPR team activation
NB, New Brunswick; ECPR, extracorporeal cardiopulmonary resuscitation; DNR, do not resuscitate; ADL, activities of daily living; OD, overdose

Expected frequency of ECPR candidates

Complete data were available for 273 patients presenting to the ED in cardiac arrest (see Appendix and Tables 2-3 for candidate breakdown).

Inclusion Criteria	Count (n)
Witnessed Cardiac Arrest	186
Age <70yo	173
No Flow <10min	146
Full Inclusion Criteria	82
Exclusion Criteria	
Unwitnessed Cardiac Arrest	87
"Asystole" at Scene	160
Suspected Etiology:	
-Uncontrolled Bleed	No Data
-Irreversible Brain Damage	No Data
-Trauma	10
Comorbidity:	
-Disability Limiting ADL	No Data
-Standing DNR Order	0
-Undergoing Palliation	6
Total Excluded ≥1 Criteria	101
-With EMS Rhythm	198

TABLE 2: Absolute numbers of candidates meeting transport criteria

EMS, emergency medical services; ADL, activities of daily living; DNR, do not resuscitate; ADL, activities of daily living

Inclusion Criteria	Count (n)
Witnessed Cardiac Arrest	186
Age <70 years old	173
No Flow <10min	146
Total Downtime <60 min	134
Refractory Arrest	257
Suspected Etiology:	
-Cardiac	No Data
-Select Non-Cardiac	No Data
Full Inclusion Criteria	80
-With Downtime	58
Exclusion Criteria	
Unwitnessed Cardiac Arrest	87
Asystole in ED	189
Suspected Etiology:	
-Uncontrolled Bleed	No Data
-Irreversible Brain Damage	No Data
-Trauma	10
Comorbidity:	
-Disability Limiting ADL	No Data
-Standing DNR Order	0
-Undergoing Palliation	6
Total Excluded ≥1 Criteria	211

TABLE 3: Absolute numbers of candidates meeting ECPR team activation criteria

ED, emergency department; ADL, activities of daily living; DNR, do not resuscitate

In all, 19 patients per year or 20.0% (95% CI 16.2-24.3%) of OHCA patients met eligibility for transportation to the ED. If an EMS rhythm criteria for asystole was included, only 10% (95% CI 7.3-13.5%) would qualify. In the ED, five patients per year, or 4.9% (95% CI 3.0-7.6%) would be eligible to receive ECPR. If local, in-house cardiac catheterization hours limitations are applied, then 9.4% (95% CI 6.8-12.9%) would be eligible for transport from the field. For ED ECPR activation, 3.0% (95% CI 1.6-5.3%) would be eligible. Further details are provided in Tables [4-5](#).

Eligible Candidates For Transport	Total Database (%)	Yearly count (mean)
Without EMS Rhythm Criteria	20.0 [95%CI 16.2-24.3]	18.5
With EMS Rhythm Criteria	10.0 [95%CI 7.3-13.5%]	9.2
Considering In-House Cath Lab Hours		
Without Rhythm	9.4 [95%CI 6.8-12.9]	8.7
With Rhythm	5.4 [95%CI 3.5-8.2]	5

TABLE 4: Eligible candidates for transport by EMS

EMS, emergency medical services

Eligible Candidates For ECPR	Total Database (%)	Yearly Count (mean)
Without Downtime Criteria	4.9 [95%CI 3.0-7.6]	4.5
With Downtime Criteria	3.8 [95%CI 2.2-6.3]	3.5
Considering In-House Cath Lab Hours		
Without Downtime	3.0 [95%CI 1.6-5.3]	2.7
With Downtime	2.4 [95%CI 1.2-4.6]	2.3

TABLE 5: Eligible candidates for ECPR

ECPR, extracorporeal cardiopulmonary resuscitation

Discussion

Despite the growing literature on ECPR practices internationally, there are no proven optimized selection criteria, and certainly none for small or medium urban centres. In this study, we have developed consensus-based criteria for ECPR and have demonstrated that the expected frequency is reasonable both in terms of skills maintenance and resource use.

Miscellaneous topics essential for the execution of a novel local ECPR program were also addressed. Mechanical CPR is an effective method for providing CPR to cardiac arrest patients and there has been evidence to show that CPR quality is greatly improved in transport while using a mechanical device [10]. Therefore, as shown in our modified Delphi, mechanical CPR devices will have a role in any future ECPR programs for OHCA. Other skills that were identified that need to be developed or sourced include rapid canalization of large blood vessels. Our Delphi showed that point-of-care ultrasound would be required for an ED-based ECPR program for vascular access and line placement.

Eligible candidates were analyzed for transport to ED by EMS, with and without the use of the EMS rhythm criterion of asystole, as historically rhythm was often categorized simply as shockable or non-shockable in the EMS data, reducing expected frequencies.

For ECPR team availability, it was agreed that initially, the program should be offered while cardiac catheterization laboratory staff are in-house. This reduces potential complicating factors of utilizing on-call resources, which can create logistical barriers and a reduction in efficiency, leading to delays. This further reduces expected candidate frequencies and hours of operation will be reevaluated during program development with the ultimate goal of unimpeded access to this service.

Finally, ECPR was never intended to be a long-term life support technique, but rather a method to extend resuscitation safely, allowing time for identifying and treating reversible causes of cardiac arrest. As such, we determined that rewarming and ECMO withdrawal should begin 24 hours post-admission, which is consistent with the existing literature [11].

Limitations

The inherent limitations of using expert opinion as a reference standard for the survey and a retrospective health records and database review are acknowledged. A contemporary literature review and liaison with international experts in the field not involved in the survey was an attempt to mitigate this. In addition, the cardiac arrest database was not designed specifically to answer this research question.

Certain conservative assumptions were applied when interpreting data. For example, patients with no cardiac arrest start time, that were witnessed arrests, were assumed to have an arrest at a time in keeping with the time of the 911 call. Total downtime was calculated using the arrival time compared with the cardiac arrest start time. Two particular limitations of the database were accounted for in the analysis. During the timeframe data was collected, all EMS in NB had automated external defibrillators, only showing shockable or non-shockable rhythms. Thus, all non-shockable rhythms were assumed asystole for secondary analysis, even though pulseless electrical activity (PEA) would be an acceptable rhythm.

In addition, we did not include patients who were not transported to hospital by EMS. Application of selection criteria to that group might impact transfer rates and subsequently impact our estimate of frequency for ECMO use.

Conclusions

Application of expert consensus-derived selection criteria for ECPR in a medium urban population centre indicates that up to one-fifth of adult out-of-hospital cardiac arrest patients would be eligible for transport to the ED for consideration of ECPR. A smaller proportion would meet the criteria for initiating ECMO in the ED. This suggests that an NB-ECPR program would not be resource-intensive yet would be sufficiently busy to maintain adequate team competency.

Appendices

1. New Brunswick Extracorporeal Cardiopulmonary Resuscitation (NB-ECPR) Criteria Selection Survey Number 1

Thank you for taking the time to participate in this survey. Your expert opinion will help the SIRH ECPR Study Group establish acceptable criteria to employ throughout our multi-phased project to develop an ECPR program.

The criteria being proposed throughout the survey are based off of the criteria currently being utilized in the rapidly expanding and developing ECPR community. Initial questions will address patient inclusion criteria. However, there are also questions for exclusion criteria, ECPR duration, and miscellaneous factors to consider that are specific to the SIRH program. Several questions will have secondary follow-up questions to help define particular parameters. There is also the option to input new parameter suggestions based on your expert opinion.

Inclusion Criteria
Please answer all questions regarding inclusion criteria for unwitnessed out of hospital cardiac arrest patients (including those occurring in the ED).

Age
*Should age be an inclusion criterion?
☐ Yes
☐ No

No Flow Time
Describes the amount of time between witnessed patient collapse/arrest to initiation of CPR.
*Should no flow time be included as an inclusion criterion?
☐ Yes
☐ No

Total Downtime
Describe the complete time between collapse/arrest to initiation of ECPR. This includes field, transport and ED time prior to starting ECPR.
*Should there be a targeted downtime in the inclusion criterion?
☐ Yes
☐ No

Refractory Arrest
Defined as no sustained ROSC (>20min) despite continued resuscitative efforts, which the removal of would result in patient death.
*Should ECPR only be offered in refractory arrests?
☐ Yes
☐ No

Initial Rhythm
*Should a patient's initial rhythm be considered in the inclusion criterion?
☐ Yes
☐ No

Suspected Etiology
*Should the suspected etiology (ie, cardiac or non-cardiac) for a patient's arrest be considered in inclusion criterion?
☐ Yes
☐ No

*From a minimum age of 18, what should the maximum age be?
☐ <65yo
☐ <75yo
☐ <70yo
☐ other _____

*What's an acceptable no flow time inclusion?
☐ <5min
☐ <10min
☐ other _____

*What is an acceptable downtime?
☐ <45min
☐ <60min
☐ other _____

*What length of time before an arrest should be considered refractory?
☐ >10min
☐ >20min
☐ >30min
☐ other _____

*Which rhythms would be acceptable? (select all that apply)
☐ Shockable (ie, VF/VT)
☐ PEA
☐ Asystole
☐ other _____

*Only suspected cardiac etiology or the addition of select non-cardiac etiologies?
☐ Only cardiac
☐ Include select non-cardiac

*Which non-cardiac etiologies are acceptable? (select all that apply)
☐ PE
☐ Drug overdose
☐ Poisoning
☐ Hypothermia
☐ other _____

Exclusion Criteria
By default, patients will be excluded if they are in hospital cardiac arrests or unwitnessed out of hospital cardiac arrests. Patients falling outside of the decided inclusion criteria will also be excluded. It has been suggested that certain non-cardiac etiologies, as well as certain patient comorbidities be utilized as exclusion criteria, which will be proposed hereafter.

Non-Cardiac Etiologies
*Which of the following, if any, would exclude patients? (select all that apply)
☐ Trauma
☐ Irreversible brain damage
☐ Submersion
☐ other _____
☐ Uncontrolled bleeding
☐ Poisoning
☐ Hypothermia
☐ None of the above

Comorbidities
*If known/identified, which comorbidities should exclude patients? (select all that apply)
☐ Severe disability interfering significantly with patient ADLs (ex, severe COPD, cirrhosis, renal failure on dialysis, etc.)
☐ Standing do not resuscitate order
☐ Patients that are undergoing palliative care
☐ None of the above
☐ other _____

Duration of ECPR
ECPR is a novel tool being utilized in acute resuscitation. It is not intended to function as chronic life support, but rather to provide a window of time to identify potentially reversible etiologies of cardiac arrest, and to allow sufficient time to correct it. Thus, it is imperative to establish the acceptable duration of use.

Several protocols currently exist in the literature, and it is suggested that the process of rewarming and weaning begin at 24 hours post admission (ex, the CHEER trial). In our Maritimes program, we are proposing that the process of rewarming and weaning begin, similarly, at 24 hours post admission. Specific weaning protocols (warming speed, rate of ECMO flow rate decrease, length of wean to de-cannulation, etc.) will be derived by the SIRH ECPR team.

*If not 24 hours, should it be shorter or longer?
☐ 12-24 hours
☐ 24-48 hours
☐ other _____

Miscellaneous
Currently, at the SIRH there are some factors that can be considered:
1. We do not, at this time, employ the use of mechanical CPR.
2. The majority of patients indicated for ECPR will have cardiac etiology and would require catheterization lab services. Currently, SIRH does not offer catheterization 24/7, which may impact activation restrictions with ECPR. However, certain non-cardiac etiologies may indicate need for emergency operations (ex, surgical thrombectomy for saddle pulmonary embolism), which would not require the cath lab.
3. SIRH ED has and employs use of point of care US (PoCUS), which would be able to identify cardiac motion &/or potential reversible etiologies.
*How important, from 0-6, are these components for implementation of ECPR at this centre?
1. Use of mechanical CPR in prehospital settings [0-6]
2. Use of mechanical CPR in ED [0-6]
3. Cath lab availability - cardiac etiology [0-6]
4. Cath lab availability - non-cardiac etiology [0-6]
5. PoCUS availability [0-6]

End
Thank you for your participation, please hit submit to conclude this survey.

FIGURE 1: Survey 1

2. New Brunswick Extracorporeal Cardiopulmonary Resuscitation (NB-ECPR) Criteria Selection Survey Number 2

Thank you for taking the time to participate in this survey. Your responses have been very helpful in identifying criteria for use in our multi-phased project to develop an ECPR program at the SIRH. I have reviewed the responses from the first survey I sent to you in August. The following are the decisions on the inclusion and exclusion based on that first round of the survey. Please indicate (yes/no) if you are happy to proceed with the majority decision where indicated.

Inclusion Criteria
Witnessed out of hospital cardiac arrest patients (including those occurring in the ED).

No Flow Time
Describes the amount of time between witnessed patient collapse/arrest to initiation of CPR. 100% of respondents agree that this should be an inclusion criterion.
•Majority selected <10min. Yes or no? ☐ Yes ☐ No
•What no flow time do you recommend

Total Downtime
Describes the complete time between collapse/arrest to initiation of ECPR. This includes field, transport and ED time prior to starting ECPR. 100% of respondents agree total downtime should be an inclusion criterion.
•There was no majority. Literature suggests initiation of ECPR should be targeted to <60min. Yes or no? ☐ Yes ☐ No
•What total downtime do you recommend

Initial Rhythm
•Majority did not feel initial rhythm should be inclusion criterion. Do you agree? ☐ Yes ☐ No
•What initial rhythms should be considered?

Suspected Etiology
•Majority agree suspected etiology should be an inclusion criterion. Do you agree? ☐ Yes ☐ No
•100% agree that cardiac etiologies and select non cardiac etiologies (PE, drug overdose, poisoning & hypothermia) should be an inclusion criterion. Yes or no? ☐ Yes ☐ No

Exclusion Criteria
By default, patients will be excluded if they are in hospital cardiac arrests or unwitnessed out of hospital cardiac arrests. Patients falling outside of the decided inclusion criteria will also be excluded.

Non-Cardiac Etiologies
100% of respondents agree that patients with uncontrolled bleeding and irreversible brain damage should be excluded.

Comorbidities
100% of respondents agree that patients with severe disability interfering significantly with ADL's, having a standing DNR order, or are undergoing palliative care should be excluded.

Duration of ECPR
With the SIRH ECPR program, we will begin the process of rewarming and weaning of ECMO 24 hours post admission.

Miscellaneous
Elaboration with regard to SIRH cath lab services. There are 24/7 services, however, they do not have 24/7 pPCI (unless indicated due to contraindications for lysis or strong indications for pPCI). Cath can be performed at any time as an on-call service, with delays inherent in team mobilization from home.

Majority of respondents did not feel that mechanical CPR was important in the prehospital setting. Majority also felt that use of mechanical CPR in hospital and cath lab availability were important considerations. 100% of respondents felt PoCUS availability was very important.

•The following are important considerations. Yes or no?
1. Use of mechanical CPR in ED [yes - no]
2. Cath lab availability (during pPCI hours) [yes - no]

End
Thank you for your participation, please hit submit to conclude this survey.

FIGURE 2: Survey 2

Thank you again for your continued support and participation. This is a 2-question addendum to the second survey in the determination of the selection criteria for ECPR in the SIRH.

The questions that have been adjusted are regarding inclusion criteria: age and definition of refractory arrest. These adjustments have been made based on further re-evaluation of the initial survey responses, as well as a recent meeting with the SIRH ECPR team. Please indicate your opinion regarding these 2 criteria.

Inclusion Criteria
Witnessed out of hospital cardiac arrest patients (including those occurring in the ED).

Age
The initial survey was unanimous in the decision to include age as an inclusion criterion. The small majority chose in favour of age <65yo. It was suggested by the closely following respondents that we widen our age parameter to allow for a greater number of potential candidates that may benefit from ECPR.
•Please select the maximum age of the inclusion criteria.
☐ <65 years old ☐ <70 years old

Refractory Cardiac Arrest
The responses on the initial survey were a significant majority stating that ECPR should not only be utilized in refractory arrest patients. This would mean that all patients that are in cardiac arrest would be candidates to being placed on ECMO during resuscitative efforts, despite the response to traditional resuscitation.

There is promising literature focused on use of ECMO in pre-arrest patients, which is termed Extracorporeal Life Support (ECLS). The purpose of this multi-phased project is to set up an ECPR program at the SIRH, which would focus on those patients that are currently in cardiac arrest. Thus, this excludes the pre-arrest patient that may benefit from ECLS.

Review of the literature and other large centre protocols, as well as the recent discussion with the SIRH ECPR team, has elucidated what is thought to be a suitable definition for refractory cardiac arrest.
•Refractory cardiac arrest: 3 cycles of CPR or 10 minutes of resuscitation with no ROSC. Do you agree with this definition (yes or no)? ☐ Yes ☐ No
•What definition do you suggest?

End
Thank you for your participation, please hit submit to conclude this survey.

FIGURE 3: Addendum to Survey 2

3. Description of data extraction process

Chart review for patients in the database with missing information included patient age, pre-arrest DNR status, terminal illness status, witnessed arrest, trauma, EMS rhythm, ED rhythm, cardiac arrest start time, time of first CPR, arrival time to hospital, and survival to admission.

After chart review, the database encompassed 395 patients. Upon review, patients who did not lose a pulse, and as such did not suffer true cardiac arrest, were excluded, leaving 371 potential candidates. Further, those with missing data points beyond the chart review were excluded from the application of criteria. There were 15 with lost charts, 15 under the age of 18, 16 with a DNR, 44 because of pre-ED return of spontaneous circulation (ROSC), 3 that had ED arrests without data, 3 that were completely blank, and 2 for unknown reasons. Thus, the criteria were applied to 273 patients, while remainders were considered ineligible. Statistics and finals number of eligible candidates were compared to the inclusive database of 371 cardiac arrest ECPR candidates.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. Horizon Health Network Research Ethics Board issued approval 2015-2132. Ethical approval was granted by the Horizon Health Research Ethics Board (REB #2015-2132). **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** This project was supported by an award from the Saint John Regional Hospital Foundation. A CAN\$75,000 award was received from the Saint John Regional Hospital Foundation to the Department of Emergency Medicine Research Team to help fund the research and equipment required to implement findings from this study. The authors have no conflicts of interest to declare. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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