Incidence of postintubation hemodynamic instability associated with emergent intubations performed outside the operating room: a systematic review

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ABSTRACT

Objective: Hemodynamic instability following emergent endotracheal intubation (EETI) is a potentially life-threatening adverse event. The objectives of this systematic literature review were to document the incidence of postintubation hemodynamic instability (PIHI), to determine the definitions for PIHI used in the available literature, and to examine factors associated with PIHI in adult patients who require EETI.

Data Source: Articles published in *Medline* (1966–August 2012).

Study Selection: This systematic review included adult, in-hospital studies of EETIs. Studies with nonemergent or pediatric patient populations were excluded.

Data Extraction: Two authors independently performed data abstraction. Disagreements were resolved by a third party. The methodological quality of included studies was assessed with the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies.

Data Synthesis: We estimated the pooled prevalence of PIHI across studies using a random effects meta-analysis. Subgroups analyzed included study design, intubation setting, geographic location of the study, physician experience, medications used for sedation, neuromuscular blockade, and definition of PIHI. Eighteen studies were analyzed, with sample sizes from 84 to 2,833 patients. The incidence of PIHI ranged from 5 to 440 cases per 1,000 intubations, with a pooled estimate of 110 cases per 1,000 intubations (95% CI 65–167).

Conclusions: PIHI was found to occur in 110 cases per 1,000 in-hospital, emergent intubations. However, heterogeneity among the included studies limits the reliability of this summary estimate. Further investigation is warranted.

RÉSUMÉ

Objectifs: L'instabilité hémodynamique consécutive à une intubation endotrachéale très urgente (IETU) est un événement indésirable potentiellement mortel. L'examen méthodique de la documentation avait pour objectifs d'établir la fréquence de l'instabilité hémodynamique après intubation (IHAI), de déterminer les définitions de l'IHAI utilisées dans la documentation et d'examiner les facteurs associés à l'IHAI chez les adultes.

Source de données: Les articles publiés dans *Medline* (1966–août 2012) ont constitué la source de données.

Sélection des études: L'examen méthodique portait sur les études ayant pour objet les IETU effectuées chez les adultes, en milieu hospitalier; les études portant sur les intubations non considérées comme très urgentes ou effectuées chez les enfants étaient écartées.

Extraction des données: Deux auteurs ont procédé, chacun de leur côté, aux résumés analytiques des données. Les divergences de point de vue ont été résolues par une tierce partie. La qualité méthodologique des études retenues a été évaluée selon l'échelle de Newcastle-Ottawa, qui permet d'évaluer la qualité des études de cohortes.

Synthèse des données: L'estimation de la prévalence globale de l'IHAI, tirée des études retenues repose sur une méta-analyse à effets aléatoires. Ont été analysés le type d'étude, le service où ont été effectuées les intubations, le lieu où ont

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été menées les études, l'expérience des médecins, les médicaments utilisés pour la sédation, le bloc neuromusculaire, et la définition de l'IHAI. Dix-huit études, dont la taille des échantillons variait de 84 à 2,833 patients, ont été examinées. La fréquence l'IHAI variait de 5 à 440 cas pour 1,000 intubations, et l'estimation de l'IHAI s'est établie, dans l'ensemble, à 110 cas pour 1,000 intubations (IC à 95% 65–167).

Conclusions: D'après l'étude, il se produit 110 cas d'IHAI pour 1,000 intubations très urgentes, effectuées à l'hôpital. Toutefois, l'hétérogénéité des études sélectionnées est venue amoindrir la fiabilité de cette estimation préliminaire; d'autres études s'imposent.

Keywords: emergency, hypotension, meta-analysis, rapid sequence intubation, systematic review

Emergent endotracheal intubation (EETI) is a potentially lifesaving procedure in critically ill patients.[1–4] These patients often require immediate resuscitation, which may result in a suboptimal intubation condition.[5] Accordingly, the incidence of adverse events associated with EETI is high in comparison with elective endotracheal intubation performed in the operating theatre.[6–10]

Adverse events during EETI range from relatively minor (local oropharyngeal soft tissue and dental trauma) to life threatening (dysrhythmias, hypoxia, hemodynamic instability, and cardiac arrest).[11–13] Hemodynamic instability in the postintubation phase is a potentially important adverse event associated with EETI that has not been fully described. Although common in clinical resuscitations, postintubation hemodynamic instability (PIHI) has not been consistently reported in studies of EETI.

PIHI may result from a multitude of factors, including patient illness and impaired hemodynamic physiology.[12] Clinicians challenged with the resuscitation of critically ill patients have viewed PIHI as a transient phenomenon of questionable significance resulting from the patient's underlying pathophysiologic state.[14,15] However, modifiable factors such as medications used to facilitate EETI, intravascular volume resuscitation prior to EETI, technical laryngoscopy skills, and aggressive positive pressure ventilation may cause or exacerbate PIHI.[11] Therefore, it is possible that EETI may contribute to poor patient outcomes due to hemodynamic instability resulting from the intubation procedure.[16] Recent studies have demonstrated the high rate of PIHI (23–44%) and an association of PIHI with increased hospital length of stay (increased 3.8 days) and mortality (increased 12%).[16,17] The investigation and identification of adverse events are particularly important with the current focus on patient safety in both emergency medicine and EETI.[9,10] Evolution of intubation strategies that minimize PIHI in critically ill patients may decrease patient morbidity and mortality.[10]

No systematic literature review has examined the risk of PIHI associated with EETIs. Therefore, we conducted this systematic review and meta-analysis to evaluate the incidence of PIHI, to determine the definitions for PIHI used in the available literature, and to examine risk factors associated with PIHI in adult patients who require EETI.

METHODS

Electronic literature search for identification of trials

A systematic search of *Medline* (1966–May 2012) was conducted to identify studies that described endotracheal intubations in emergent settings and associated adverse events, with a primary interest in the incidence of PIHI. The strategy combined the terms *hypotension*, *blood pressure*, *hemodynamic*, *hemodynamic instability*, *emergency medicine*, *rapid sequence intubation*, *endotracheal intubation*, *extubation*, *airway management*, *resuscitation*, *artificial respiration*, *respiratory insufficiency*, and *obstructive lung diseases* to identify studies related to intubation. In addition, the terms *epidemiology*, *epidemiologic*, *observational*, *case control*, *cohort*, *follow-up*, *longitudinal*, *retrospective*, *and cross-sectional* were used to identify both observational studies and randomized controlled trials. The bibliographies of all identified studies were reviewed to identify any additional relevant reports, and expert consultation was sought to identify any remaining unidentified studies. Studies with a full publication in either English or French were included. An online appendix to this article lists the full details of the search strategy used (Appendix 1).

Eligibility criteria and study selection

Randomized trials and observational studies (retrospective or prospective) that evaluated the incidence of hemodynamic instability after in-hospital EETIs in adults (≥ 17 years of age) were eligible. No restrictions

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were placed on patient diagnosis or indication for intubation. All drugs and dosage regimens of drugs used during the pretreatment, induction/sedation, and neuromuscular blockade stages of EETI were considered. Studies were required to report on the frequency of hemodynamic instability observed after intubation. Studies that described intubations in the operating theatre or other intubations considered elective were excluded. One author (D.B.) independently reviewed all citations retrieved from the electronic search to identify all potentially relevant trials for this review, and two authors (D.B., B.H.) independently reviewed all candidate articles during the process of final selection. The bibliographies of included articles were also searched for additional studies not identified by the electronic search. Disagreements regarding eligibility were resolved by consensus following consultation with a third party (R.G.).

Data extraction

A standardized data abstraction form was developed that captured the following information from each included study: patient demographics (gender, age), country of study origin, patient population/setting for intubations, clinical indications requiring intubation, medications used for pretreatment/sedation/neuromuscular blockade of intubation, medical staff performing intubation (and corresponding experience levels), number of patients included in the study (and number analyzed), intubation success rate, study duration, observed rate of hypotension (and corresponding definition, if provided), and rates of any other reported complications. A "comprehensive definition" of PIHI was defined as one that included both the blood pressure below which a patient was considered hemodynamically unstable and the time period between intubation and the onset of the hypotensive event. Studies that used a definition that did not fulfill both of the above criteria were considered to have a "noncomprehensive definition" of PIHI.

Two authors (B.H., J.L.) independently performed data abstraction. Disagreements in abstracted elements were settled through involvement of a third party (R.G.) if consensus agreement could not be achieved between the two reviewers. The methodological quality of included studies was assessed with the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies, which allocates points in three distinct areas: selection (maximum 4 stars), comparability of cases (maximum 2 stars), and outcome (maximum 3 stars). Detailed evidence tables summarizing all of the collected information were compiled (Appendix 2).

Evidence summary and data analysis

A random effects meta-analysis was employed to estimate the pooled incidence of PIHI across the included studies. Statistical and clinical heterogeneity was anticipated during the planning of this systematic review, and to address this concern, specific subgroups for further analysis were selected a priori based on important characteristics chosen by the investigative team. These subgroups included study design (randomized controlled trial [RCT], prospective cohort, retrospective cohort), hospital setting (emergency department [ED], in-hospital ward, both), study location (Asia, North America [Canada, United States], Europe), clinical experience of medical personnel (attending physician, trainees), and definition used for PIHI (comprehensive, noncomprehensive).

We also hypothesized that the use of some medications (etomidate and ketamine) may be associated with a decreased incidence of PIHI, whereas others (propofol) may be associated with an increased incidence of PIHI.[18,19] Due to substantial variability in the reporting of medication use in EETI, medications were categorized by the percentage of patients in the study receiving a given medication ($< 10\%$, 10–49%, $\geq 50\%$). Medications considered included propofol, fentanyl, etomidate, ketamine, thiopental, midazolam, and the neuromuscular blocking medications (NMBMs) succinylcholine and rocuronium.

Cochrane Q and I^2 measures of heterogeneity were used to examine the presence of statistical heterogeneity for the primary and subgroup analyses and to guide the appropriateness of data synthesis. In general, meta-analyses are performed to bring together data from studies addressing similar research questions by combining the data in a quantitative manner. These heterogeneity measures are often used to identify situations where the effects being examined may appear to be different across studies for reasons other than random chance alone. For the purposes of our analyses, a Cochrane Q p value of 0.1 or less and an I^2 value of 30% or larger were considered to indicate the presence of significant heterogeneity where differences for reasons other than chance may be present. In such cases, consideration of findings from subgroup analyses

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as described above can be helpful to potentially identify the source(s) of study-to-study differences observed.

RESULTS

Quantity of research available

A total of 3,171 citations were identified for review from the initial literature search, with 34 potentially relevant citations retrieved for consideration after independent review of all citations by one reviewer (B.H.) (Appendix 3). In addition, 20 articles identified from bibliographic review were assessed for eligibility, resulting in 54 manuscripts reviewed in full. Of the 54 articles, 36 were excluded based on patient population (n = 24), no discussion of complications (n = 6), or being a review article (n = 6). Eighteen articles were retained for inclusion.[8,9,16,17,20–33] Appendix 4 summarizes the clinical characteristics of the included studies. Appendix 5 outlines the epidemiologic and methodological traits of the studies included in the analysis.

Study characteristics

Of the 18 included studies, 17 were observational in nature, 12 being prospective evaluations and 5 retrospective (see Appendix 4 and Appendix 5). Only one RCT was identified that met our inclusion criteria.[20] For the purposes of our analysis, each of the three treatment arms of the RCT was analyzed as a separate cohort of patients. The majority of included studies (16 of 18, 88.8%) were single-centre investigations and described intubations performed exclusively in hospital EDs (14 of 18, 77.8%), whereas the remaining studies involved patients from the intensive care unit (ICU) (2 of 18, 11.1%) or a combination of EDs and ICUs (2 of 18, 11.1%). Sample sizes ranged from 84 to 2,833 patients (median n = 207), and the median year of publication was 2003 (range 1994–2012). The majority of studies were performed in North America (Canada, n = 6; United States, n = 6), and these studies included the majority of patients enrolled (n = 3,430). Five studies originated in Asia and three in Europe.

Study quality and variability

In terms of study quality using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies, the majority of included studies scored 3 of 4 stars in selection of patients (15 of 18 studies), with 2 scoring 4 stars. Two studies scored 2 of 2 stars in comparability, whereas 4 scored 1 of 2 stars, with the remaining scoring 0 stars (see Appendix 2). All studies scored the maximum 3 stars for outcomes. The lone RCT was not assessed with this scale.[20]

Substantial variability in the key data points was observed. The data reported in the reviewed studies varied in terms of study population, intubator experience, and medications used to facilitate intubations. Most studies included both medical and surgical patients, with differing pathophysiologic states and reasons for EETI (see Appendix 4 and Appendix 5). In addition, intubations in cardiac arrest patients were included in some studies.[9,24,25,28–30] Sixteen studies included data from intubations performed by both attending and resident physicians, whereas three were limited to attending physicians only. One study did not report data on intubator experience.[23]

Assorted medications were used to facilitate EETI in the included studies; these included a variable combination of propofol, midazolam, fentanyl, etomidate, ketamine, and/or thiopental as a standard intubation protocol between studies was not found. In addition, some studies reported the use of NMBMs (succinylcholine and/or rocuronium), but the use of these medications varied as well (see Appendix 4 and Appendix 5).

There was no standard definition of PIHI used in the included studies. Most studies (n = 14) identified a systolic blood pressure (SBP; < 65–95 mm Hg) threshold below which a patient was considered hypotensive.[8,9,16,17,21–24,27,29–33] Only 10 studies reported a comprehensive definition of PIHI, with a temporal relationship of blood pressure reduction to EETI from 5 minutes to 2 hours.[8,9,16,17,20,23,29,31–33]

Pooled incidence of PIHI

Overall, the pooled incidence of PIHI was 110 cases per 1,000 intubations (11%, 95% CI 65–167) (Figure 1). PIHI varied widely across the studies, with a range from 10 to 440 cases per 1,000.

PIHI incidence in a priori subgroups

Study design

The single RCT included in this review demonstrated a PIHI rate of 240 cases per 1,000 intubations (95% CI 150–380), whereas prospective epidemiologic studies

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Study	Year	Design	Statistics for each study				Study Duration	Events per 1,000 (95% CI)
			Event rate	Lower limit	Upper limit	n/N		
Sivilotti-A	1998	RCT	0.34	0.20	0.53	10 / 29	13 months	345 (197-531)
Sivilotti-B	1998	RCT	0.14	0.05	0.32	4 / 28	13 months	143 (55-324)
Sivilotti-C	1998	RCT	0.24	0.12	0.43	7 / 29	13 months	241 (120-427)
Griesdale	2008	PC	0.10	0.06	0.16	13 / 136	5 months	96 (56-158)
Jaber	2006	PC	0.26	0.21	0.31	65 / 253	6 months	257 (207-314)
Reid	2004	PC	0.18	0.13	0.24	37 / 208	6 months	178 (132-236)
Mort	2004	PC	0.39	0.30	0.48	44 / 114	119 months	386 (301-478)
Choi	2004	PC	0.11	0.07	0.17	18 / 160	23 months	113 (72-171)
Wong-A	2004	PC	0.04	0.03	0.06	45 / 1068	48 months	42 (32-56)
Graham	2003	PC	0.03	0.02	0.05	25 / 732	24 months	34 (23-50)
Marvez	2003	PC	0.01	0.01	0.02	12 / 1320	48 months	10 (5-16)
Tam	2001	PC	0.01	0.00	0.04	3 / 207	6 months	14 (5-44)
Tayal	1999	PC	0.00	0.00	0.02	2 / 417	24 months	5 (1-19)
Sakles	1998	PC	0.00	0.00	0.02	3 / 610	12 months	5 (2-15)
Franklin	1994	PC	0.29	0.20	0.39	24 / 84	12 months	286 (199-391)
Green	2012	RC	0.44	0.38	0.51	96 / 218	16 months	440 (380-510)
Heffner	2011	RC	0.24	0.19	0.28	79 / 336	12 months	240 (190-280)
Lin	2008	RC	0.19	0.13	0.26	28 / 149	6 months	188 (133-259)
Wong-B	2003	RC	0.19	0.13	0.26	27 / 142	36 months	190 (134-263)
Dufour	1994	RC	0.11	0.07	0.16	24 / 219	24 months	110 (75-158)
OVERALL			**0.11**	**0.065**	**0.167**	**565 / 6459**		**110 (65-167)**

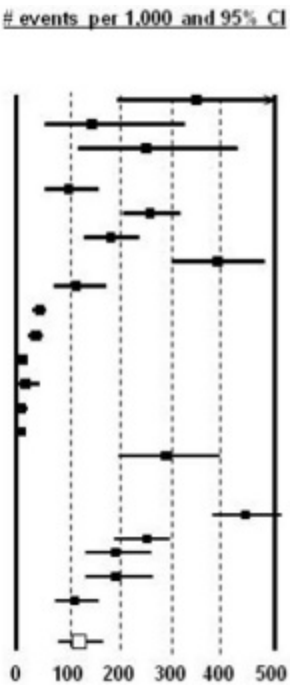

Figure 1. Frequency of postintubation hemodynamic instability (PIHI) in included studies by study design. RCT = Randomized controlled trial; PC = Prospective Cohort; RC = retrospective cohort.

had a rate of PIHI of 60 cases per 1,000 intubations (95% CI 30–120) and retrospective studies 160 cases per 1,000 intubations (95% CI 110–220) (see Figure 1).

Hospital location

The incidence of PIHI varied according to hospital location as subgroup analysis yielded pooled incidences of 90 cases per 1,000 intubations (95% CI 50–150), 160 cases per 1,000 intubations (95% CI 60–390), and 270 cases per 1,000 intubations (95% CI 110–510) in EDs, in-hospital ward, and combined ED/in-hospital ward, respectively (Figure 2).

Geographic location

The pooled incidence rates were 210 cases per 1,000 intubations (95% CI 100–380) in Canadian studies, 120 cases per 1,000 intubations (95% CI 40–340) in European studies, 80 cases per 1,000 intubations (95% CI 40–180) in Asian studies, and 50 cases per 1,000 intubations (95% CI 10–180) in American studies (Figure 3).

Intubator experience

Attending physicians were associated with an estimated incidence of 50 cases per 1,000 intubations (95% CI 30–100), whereas attending physicians working with resident physicians were associated with an incidence of 120 cases per 1,000 intubations (95% CI 70–190) (Figure 4). One study with an estimated incidence of 110 cases per 1,000 intubations (95% CI 70–170) did not identify the intubator.

Definition of PIHI

When exploring the impact of clinical definition of PIHI, studies with a comprehensive definition (blood pressure threshold and a temporal relationship to EETI) were associated with a pooled incidence of 170 PIHI cases per 1,000 intubations (95% CI 11–260), whereas those with a noncomprehensive definition had an incidence of 60 PIHI cases per 1,000 intubations (95% CI 20–130) (Figure 5). There were still considerable ranges of estimates within both those with a comprehensive definition (minimum 5 cases per 1,000, maximum 440 cases per 1,000) and those with a noncomprehensive definition (minimum 5 cases per 1,000, maximum 386 cases per 1,000).

Association of PIHI with medication use

Figure 6 displays the incidence of PIHI within the defined categories (< 10%, 10–49%, > 50%) of medications administered to facilitate EETI. Substantial variability in the incidence of PIHI was found when medications were considered, yet due to the wide and overlapping 95% CI, no definite conclusions can be drawn regarding the influence of the medications administered.

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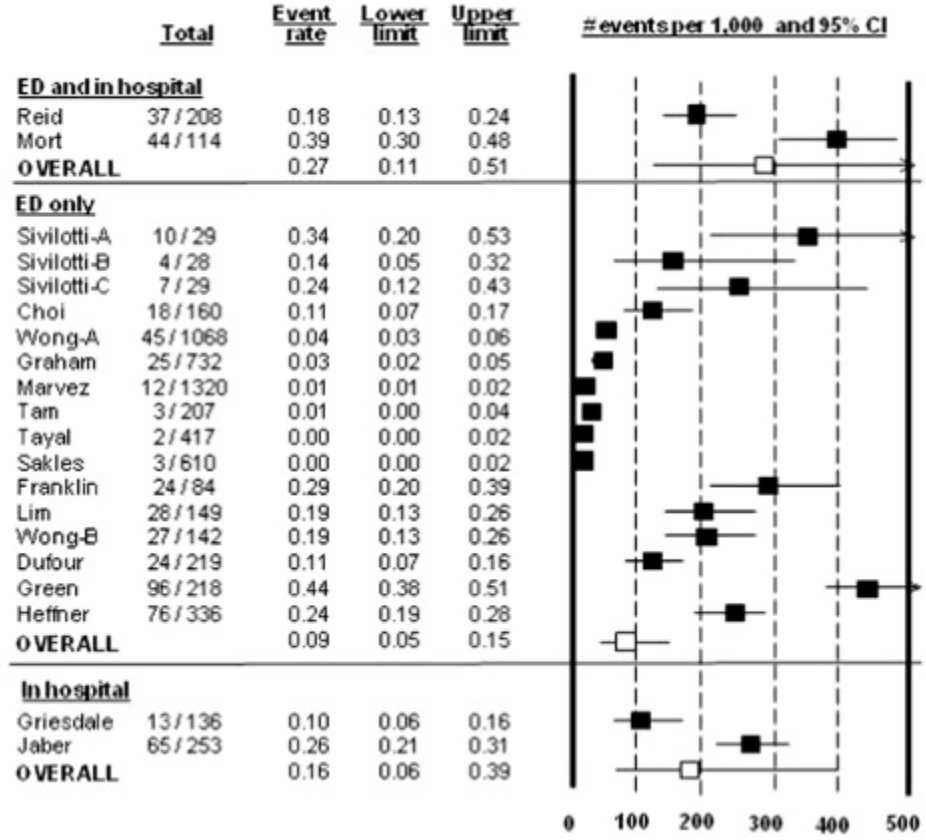

Figure 2. Postintubation hemodynamic instability (PIHI) and hospital location. ED = emergency department.

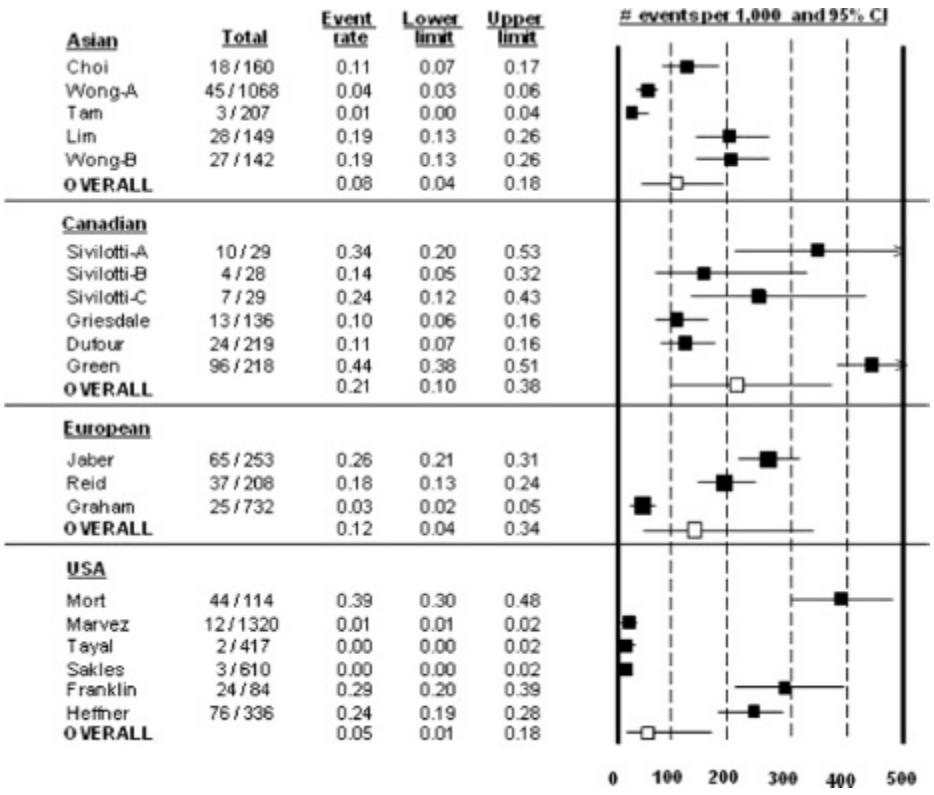

Figure 3. Postintubation hemodynamic instability (PIHI) and geographic origin.

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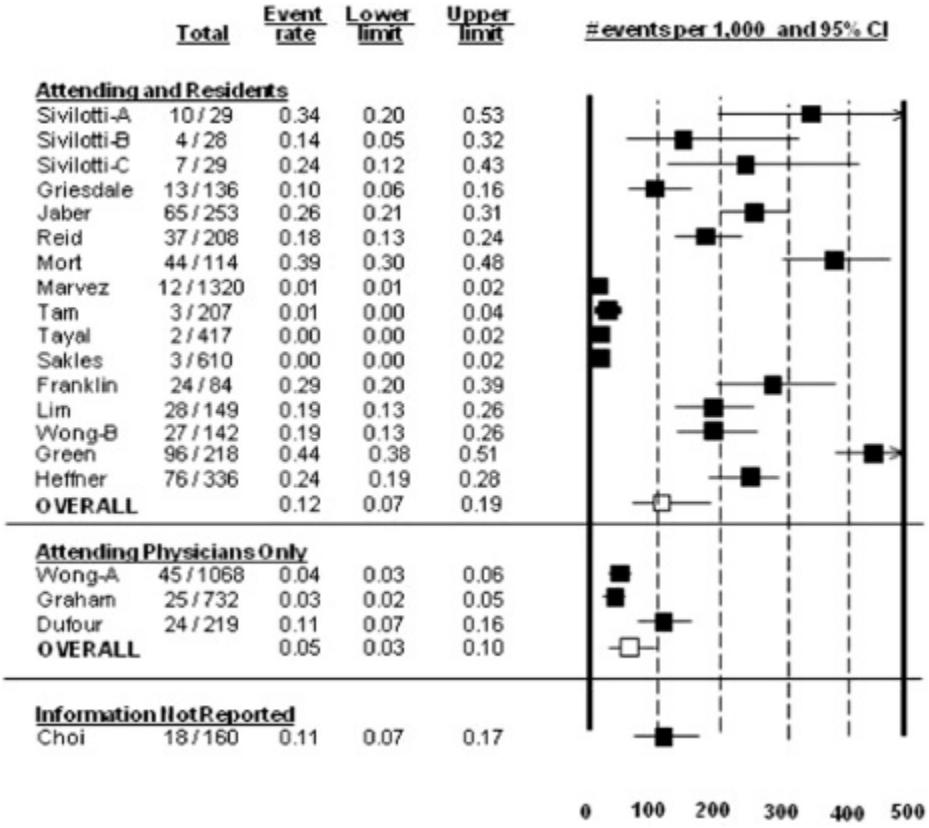

Figure 4. Postintubation hemodynamic instability (PIHI) and intubator experience.

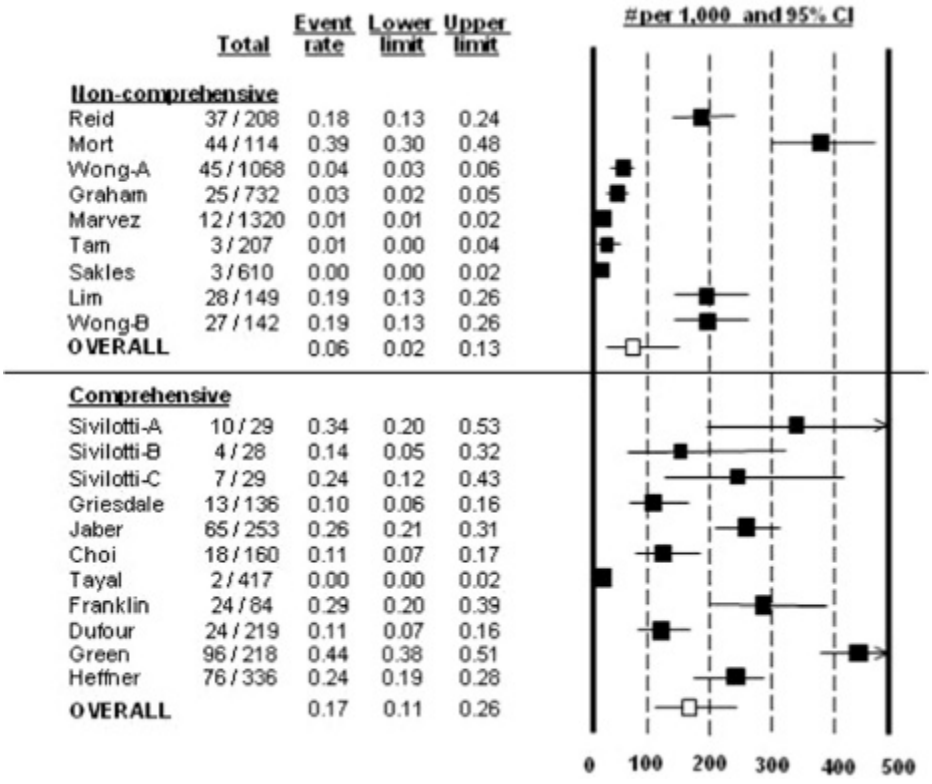

Figure 5. Definition of postintubation hemodynamic instability (PIHI).

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Drug/Category	# studies	n/N	Event rate	Lower limit	Upper limit	# per 1,000 and 95% CI
Propafol						
<10%	3	102/1318	0.13	0.02	0.46	130 (20-460)
10-49%	3	198/669	0.28	0.16	0.45	281 (158-450)
≥50%	0	NA	NA	NA	NA	NA
Midazolam						
<10%	1	37/208	0.18	0.13	0.24	180 (130-240)
10-49%	6	233/2126	0.11	0.04	0.30	110 (40-300)
≥50%	6	74/733	0.11	0.06	0.19	110 (60-190)
Fentanyl						
<10%	4	94/1806	0.04	0.01	0.22	40 (10-220)
10-49%	4	222/898	0.23	0.12	0.39	230 (120-390)
≥50%	1	4/28	0.14	0.06	0.32	140 (60-320)
Etomidate						
<10%	3	84/1693	0.04	0.01	0.16	40 (10-160)
10-49%	3	205/585	0.36	0.25	0.48	360 (250-480)
≥50%	3	100/1106	0.06	0.001	0.24	60 (1-240)
Ketamine						
<10%	4	87/2303	0.02	0.01	0.09	20 (10-90)
10-49%	2	41/285	0.14	0.07	0.26	140 (70-260)
≥50%	0	NA	NA	NA	NA	NA
Thiopental						
<10%	2	68/460	0.07	0.01	0.62	70 (10-620)
10-49%	3	83/739	0.10	0.02	0.33	100 (20-330)
≥50%	1	10/29	0.35	0.20	0.53	350 (200-530)
Succinylcholine	0					
<10%		NA	NA	NA	NA	NA
10-49%	5	194/1713	0.16	0.06	0.34	160 (60-340)
≥50%	10	265/2301	0.10	0.05	0.19	100 (50-190)
Rocuronium						
<10%	3	92/1389	0.07	0.01	0.39	70 (10-390)
10-49%	2	109/354	0.23	0.04	0.68	230 (40-680)
≥50%	1	28/149	0.19	0.13	0.26	190 (130-260)

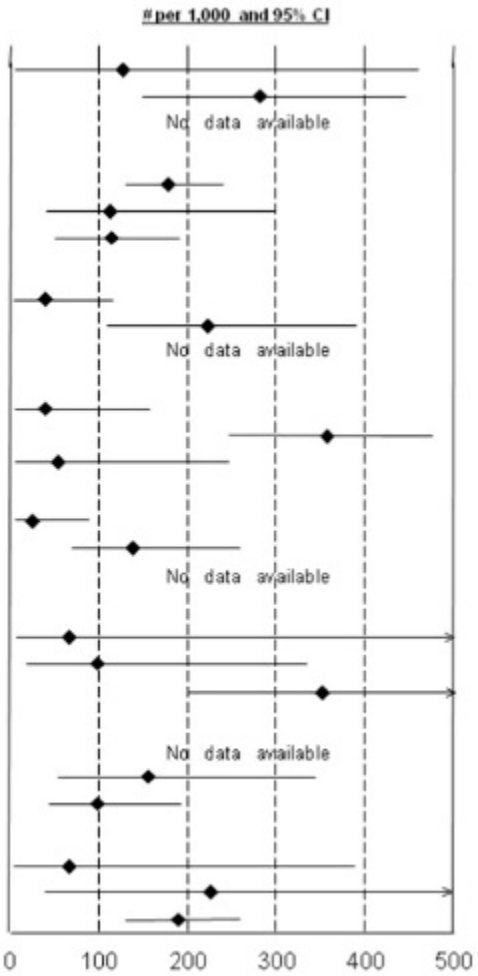

Figure 6. Postintubation hemodynamic instability (PIHI) variability with medications used to facilitate intubation, grouped by the percentage of patients in the study receiving a given medication (< 10%, 10–49%, > 50%). NA = not applicable.

PIHI incidence in association with study size

The impact of study size was assessed in a post hoc analysis. Studies were evaluated within the groups of < 100 subjects, 101 to 500 subjects, and > 500 subjects. In this analysis, PIHI was found to occur in 269 cases per 1,000 (95% CI 204–377 per 1,000) in studies with < 100 subjects; 149 cases per 1,000 (95% CI 100–218 per 1,000) in studies with 101 to 500 subjects; and 18 cases per 1,000 (95% CI 8–40 per 1,000) in studies with > 501 subjects.

Assessment of heterogeneity

Significant heterogeneity between studies was determined in both the pooled incidence of PIHI and within predetermined subgroups based on Cochrane Q and the I^2 calculations. Therefore, the variable rates of PIHI identified might be affected by factors other than chance alone.

DISCUSSION

PIHI is a common event after EETIs, with an overall pooled incidence of 110 cases per 1,000 intubations based on the available literature. We could not determine an observable association between PIHI and study design, geographic location, in-hospital location of EETI, experience level of the intubator, or comprehensiveness of the definition of PIHI used. We also did not identify a clear association between medications used to facilitate intubation and the development of PIHI based on the available studies. Unfortunately, few studies described the potential impact of PIHI on patient outcomes, such as mortality and organ dysfunction.[16,17]

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PIHI is one of a multitude of adverse events that may occur during EETI, and clinicians charged with the management of critically ill patients often tailor their intubation strategies to avoid or minimize hypotension.[11,12,19] However, PIHI has received relatively little attention, despite data indicating that hypotension has been associated with poor patient outcomes in other populations with a lower severity of illness and recent data indicating an association between PIHI and patient mortality.[16,17,34] Accordingly, additional hypotension secondary to the EETI procedure in a patient population that is often in a physiologically deranged state may lead to adverse patient outcomes, such as cardiac arrest and multiorgan dysfunction in the short term and prolonged ICU length of stay in the longer term.[16,17] In other words, although potentially lifesaving in many cases, it is plausible that the benefits of EETI may be reduced by the resultant hemodynamic instability secondary to this procedure.[10] PIHI may be a significant patient safety factor whose importance has not been recognized previously. An accurate estimation of the incidence of PIHI is required to provide the necessary background data for further research into the pathophysiology, risk factors, and association of PIHI with important patient outcomes.

We found that the incidence of PIHI varied widely, even within a priori selected subgroups. To some extent, the variability of the reported incidence of PIHI likely reflects the primary focus of the available studies, which for the most part was not to determine the incidence of PIHI. In fact, only four studies had the description of PIHI as their primary objective, with the other studies only recording PIHI as part of their data set.[16,17,21,31] Factors such as study design, hospital setting, geographic location, and physician experience were determined a priori as potentially important variables that may influence the incidence of PIHI. However, although our point estimates differed when these subgroups were considered, the correspondingly wide 95% CI and heterogeneity of the available data limit our ability to confidently detect the impact of these variables.

Previous studies have described the impact of physician experience on EETI and other adverse events, and it is plausible that physician skill is an important determinant of PIHI.[8–10] However, the data identified here do not clearly establish the importance of physician skill, with the available studies having divergent results. It is possible that these factors, and the other subgroups assessed, may indeed influence the incidence of PIHI as our ability to combine the available data is limited. Our post hoc analysis of study size demonstrated a trend toward a lower incidence of PIHI in larger studies. However, testing for heterogeneity indicates the possibility of systematic differences between studies that may have resulted in the observed differences in rates of PIHI. In fact, this was expected to some extent as adverse events of EETI have not been a focus of most research in this area. EETI studies have primarily evaluated intubation success rather than the assessment of adverse events and their relation to overall patient outcomes. This and the variable study designs included in the systematic review likely account for our findings.

Interestingly, no standard definition of PIHI exists as a blood pressure threshold below which a low blood pressure causes patient harm has not been determined. Similarly, the importance of the duration of hypotension is unknown, although evidence indicates that prolonged hypotension is associated with corresponding worse patient outcomes.[34] It is possible that any PIHI is an important determinant of patient mortality, especially in this patient population.[16,34] These issues are highlighted in our review as only 10 of 18 studies (55.5%) described a definition of PIHI that included a blood pressure threshold and its temporal relationship to EETI, which is required to associate PIHI with the intubation procedure. All definitions in the included studies differed from each other, although a SBP below 90 mm Hg was a common threshold.[8,9,16,17,20,23,29,31,33] PIHI varied when the definitions were considered, with the point estimate of PIHI incidence almost tripling when a comprehensive definition as opposed to a noncomprehensive definition was used, although we are limited in drawing firm conclusions. In our opinion, PIHI should use a blood pressure threshold below which constitutes clinically relevant hemodynamic instability (SBP $<$ 90 mm Hg, or mean arterial blood pressure $<$ 60 mm Hg, or the use of a vasopressor medication) and a temporal relationship to the intubation procedure (within 15 to 30 minutes). Hypotension that occurs beyond this time frame is likely a result of other etiologies.

Medications administered to facilitate EETI are often considered an important contributor to PIHI, and some medications, such as etomidate, are used specifically for its perceived cardiovascular stability during EETI.[15,18,19,35] In our analysis, medications were divided into groups depending on the frequency with

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which the medication was reportedly used in the study population. Interestingly, we were unable to demonstrate any medications that were associated with the development of PIHI, although we were again limited in our ability to do so because of the manner in which the data were reported in the studies. Even medications such as propofol, which is widely considered a prominent factor in hemodynamic instability when rapidly administered during EETI,[36,37] was not associated with PIHI, nor was etomidate associated with a reduced incidence of PIHI. The available data did not allow for analysis of dosing regimens or the impact of certain medication combinations.

As we have noted, the major limitation of this systematic review is the variability of the data in the original studies. Although we are confident that our search strategy, data acquisition, and analysis are sound and complete, we are cautious in our interpretations because of the variable primary objectives, study designs, lack of standard intubation regimens, lack of standard adverse events definitions (including PIHI), and incomplete reporting of the data in the studies that met our inclusion criteria. There are likely several potential confounding variables, such as patient illness, comorbidities, and physician experience, to name a few, that may have implications for our analyses. We also limited our study to include only those studies published in English or French, which may have introduced a selection bias. Given these limitations, the pooled incidence of PIHI of 110 cases per 1,000 intubations should be viewed as the best estimate of PIHI available, yet with the caveat that there is a paucity of high-quality data on the true incidence and impact of PIHI.

Indeed, further studies are required to accurately determine the true incidence of PIHI, the factors associated with its development, and its impact on patient outcomes. It is plausible that PIHI is an important and underappreciated adverse event of EETI and that it may directly impact on patient outcomes. Future studies on EETI should evolve from the historical primary outcome of "intubation success" to the evaluation of the intubation procedure as a whole, including all related adverse events. Evaluation of long-term patient outcomes (90-day mortality) with this view would provide a clearer representation of the potential benefits and areas for improvement in patient safety during EETI. Both epidemiologic and interventional clinical trials looking at factors such as preintubation resuscitation, intubator experience, medication use, and adverse events, among other potential variables, would clarify the outcomes of patients requiring EETI in emergency medicine. Accordingly, standard definitions of adverse events should be developed, including PIHI.

CONCLUSION

Based on the available literature, the incidence of PIHI in EETI is between 5 and 440 cases per 1,000 intubations, with an overall pooled incidence of 110 cases per 1,000 intubations. Variability in reporting limits an accurate determination of the incidence of PIHI and the factors that may be associated with the development of PIHI. Further efforts are required to accurately determine the incidence of PIHI and identify risk factors and outcomes associated with PIHI.

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