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REVIEW

The prevalence of pulmonary embolism in chronically paralyzed subjects: a review of available evidence

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Study design: Qualitative systematic review.
Objectives: To examine the validity of the prevailing notion that pulmonary embolism (PE) is rare in the chronic spinal cord injury (SCI) population.
Setting: USA.
Methods: Review surveys of adult SCI subjects >2 months after injury in which PE has been looked for and its prevalence estimated.
Results: A total of 16 surveys of chronic SCI subjects published between 1956 and 2009 offered data on PE prevalence. Two autopsy surveys, 178 subjects paralyzed >2 months, revealed no PE. Eleven surveys of the cause of death, 3193 subjects paralyzed 1–25 years, revealed PE in 2.1%. Two surveys of survivors of SCI, 5761 subjects paralyzed 1–25 years, revealed PE in 0.4%. Our survey of 112 subjects paralyzed 1–50 years before death, revealed PE in 21 (18.7%), based on autopsy, imaging, clinical and electrocardiographic evidence. In 7 (33%) of the 21 subjects with PE, pulmonary hypertension by transthoracic echocardiography was detected, indicating recurrent and/or unresolved PE.
Conclusion: PE is not infrequent in the chronic SCI subject; but its presentation may be subclinical; and its apparent recurrence may lead to pulmonary hypertension.
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Keywords: spinal cord injury; pulmonary embolism; pulmonary hypertension; right bundle branch block

INTRODUCTION

Acute spinal cord injury (SCI) has long been recognized as a major risk factor for pulmonary thromboembolism (PE), but PE has generally been considered rare beyond the first 3 months of paralysis.[1,2] Since these autopsy surveys of nearly 50 years ago, a concept that the chronic SCI subject has developed some protection from PE has prevailed. However, two recent deaths from late PE in chronic SCI subjects at our hospital have led us to reexamine the question.[3,4] We are therefore reviewing surveys for PE, including our own,[5] to examine the validity of the prevailing notion that PE is rare in these subjects, and to discuss the problems of recognition and management of PE in this population.

PE VS DEEP VENOUS THROMBOSIS (DVT)

Although autopsy studies have demonstrated that the DVT of lower extremities is the common source of PE, this review is limited to PE as more relevant clinically.[6,7] The reasons are as follows. First, clinical experience in the able-bodied reveals that the largest PE are released before DVT is detectable on physical examination.[8] Second, the natural course of DVT is to grow proximally within the deep venous system of the leg with loose attachments to the vein walls and become susceptible to release. With time these thrombi dissolve or become organized and firmly attached to the vein walls. The tracking of angiographic contrast on venography disappears,[9] and the risk of the release of PE is diminished by the time DVT becomes clinically manifest. Third, PE can occur even before DVT is detected by daily radioiodinated fibrinogen leg scanning, the clinically silent DVT being confirmed by venography.[10] Fourth, experimentally induced phlebitis (jugular vein of a dog) can release large PE within 1 h of the thrombus induction, the PE size tapering as the residual thrombus diminishes with time.[11] Although PE may be more difficult to recognize in the chronic SCI subject, as will be discussed, it is the more significant manifestation of the thromboembolic complication of this patient population.

SEARCH FOR SURVEYS OF PE IN CHRONIC SCI

Medical literature was searched through PubMed for the terms 'pulmonary embolism', 'spinal cord injury' and 'survey'. Those articles that surveyed for PE in SCI subjects who were chronic were selected and were also perused for further references. Excluded were surveys in which the subjects were not adult, the duration of paralysis was not stated or was <2 months, the diagnosis of PE was not specified, or the data were redundant.

PE PREVALENCE IN CHRONIC SCI

A total of 27 relevant surveys were found in papers published from 1956 to 2009. Nine were excluded for failure to designate PE as a diagnosis and two because of an unstated duration of paralysis. The remaining 16 are listed in Table 1.[1,2,5,11–23] The table shows the absence of PE in autopsy surveys, a very low prevalence of PE as a cause of death or even in survivors of SCI registered for continuing care, but a relatively high prevalence of PE in the records screened by electrocardiogram (ECG). Reasons for these discrepancies are discussed below.

The two autopsy surveys listed reported that PE was not found in a total of 178 examinations, the experience that presumably led to the

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Table 1 Onset and prevalence of pulmonary embolism (PE) in chronic spinal cord injury (SCI)

Author	*Year*	*Surveyed records*	N	*Duration of paralysis*	*PE (%)*
Tribe[1]	1963	Autopsy	122	>2 months	0
Wolman[2]	1964	Autopsy	56	>2 months	0
Lord[12]	1956	Death	22	7 years	2 (11)
Nyquist[13]	1965	Death	258	8–20 years	3 (1)
Freed[14]	1966	Death	44	1–22 years	2 (5)
Price[15]	1973	Death	11	8–31 years	0
Naso[16]	1974	Survivors	17	'Chronic'	0
Geisler[17]	1977	Deaths	428	'Years'	0
Hackler[18]	1977	Deaths	445	1–25 years	2 (<1)
Geisler[19]	1983	Deaths	194	2–16 years	0
Rish[20]	1997	Deaths	43	1–25 years	2
McKinley[21]	1999	Survivors	5744	1–25 years	24 (0.4)
DeVivo[22]	1999	Deaths	1543	1–25 years	49 (0.3)
Soden[23]	2000	Deaths	195	>1.5 years	0
Zelig[24]	2000	Deaths	10	>20 years	0
Frisbie[5]	2009	Deaths[a]	112	1–50 years	21 (18.7)

[a]Electrocardiographic survey of all records taken during paralysis. The presence of a right bundle branch block pattern on electrocardiogram (ECG) triggered a focused review for evidence for PE by available autopsy, imaging, clinical review, or other ECG evidence.

belief that PE is rare in the chronic SCI population. However, autopsy surveys may underestimate PE for the following reasons. First, earlier PE, beyond the acute SCI period but before death, may have fragmented and resolved. Second, dissection of the subsegmental arteries or microscopic examinations of sections, which can increase the yield of PE at autopsy, may not have been carried out.[25] The following synopsis of a previously reported case suggests that even small PE detected on a careful autopsy can indicate significant, even fatal PE events.[4]

A chronically tetraplegic man came to autopsy after a long course of vague complaints ending in apprehension, hypotension and cardiovascular collapse. Autopsy revealed no gross PE, even in subsegmental arteries. Microscopic examination, however, revealed plugging of pulmonary arterioles with thrombotic material–some fresh, some scarred and some with neovascularization. Furthermore, the right ventricular wall of the heart was thickened. This case suggested that chronic, recurring PE causing longstanding pulmonary hypertension, right ventricular hypertrophy and eventually death is not immediately apparent at autopsy.

In contrast to the surveys relying exclusively on autopsy examination are the surveys for PE as the cause of death or for PE morbidity among survivors–diagnosed clinically or confirmed with ventilation-perfusion lung scan or pulmonary angiography but always treated with anticoagulation. McKinley *et al.*[21] reported more PE, although the prevalence was low (Table 1). These reports are also underestimates. Two reasons can be suggested. First, the clinical signs and symptoms of PE are obscured in SCI. The predominant PE symptom, dyspnea,[26] may be ignored as dyspnea is itself a common complaint of tetraplegic subjects.[27] Hypotension may not be considered as labile blood pressure and low blood pressure are common in the tetraplegic subject.[28,29] The pleuritic chest pain of pulmonary infarction may not be noticed by the subject with an insensate chest wall. The apprehension of PE is often misinterpreted as psychological, despite its documentation in medical reviews.[26] Second, the level of suspicion for PE may be low due to the impressions derived from the earlier autopsy reports of chronic SCI subjects. A diagnosis of PE may not be considered or pursued for these reasons.

Far exceeding the PE estimates of previous clinical surveys, however, is the most recent report, our retrospective record examination of deceased subjects, which utilized records of annual ECG.[5] The presence of right bundle branch block (RBBB) was adopted as a screening tool for PE because major and/or recurrent PE can lead to pulmonary hypertension and right ventricular enlargement, resulting in transient or persistent RBBB. When subjects with myocardial infarction and chronic obstructive pulmonary disease, the other common causes of RBBB, were excluded, further record review ruled in PE by autopsy reports, description of a known source of PE, lung scanning, an intermittency of RBBB, or other ECG signs. A prevalence of 18.7% for the duration of SCI, accounting for about 3% of deaths, was reported. Even this may be an underestimate because minor PE events can occur without RBBB on ECG and might have been missed in our survey. This high prevalence is explainable by the screening for subclinical PE in the chronic SCI subject.

COURSE OF PE

The prevailing notion is that the course of PE is one of diminishing prevalence with longer duration of SCI, according to the large survey of survivors of SCI by McKinley *et al.* and the extensive review of the cause of death after SCI by DeVivo *et al.*[21,22] The diagnoses were largely clinical and the longest follow-up periods were 25 years. However, the course of PE appears to be one of increasing prevalence with longer duration of paralysis as determined by electrocardiographic survey.[5] The diagnosis of PE that was suspected by RBBB on ECG, was confirmed by autopsy, imaging, clinical or ECG evidence. The follow-up period, SCI onset to death, was as long as 50 years. Although it is true that PE soon after SCI is larger, clinically apparent and sometimes fatal, its prevalence does not diminish with time. With increased SCI survival the PE continues but is smaller, clinically silent and a cause of pulmonary hypertension.

In support of the concept that PE may be of small size in the chronic SCI subject, it has been noted in venographic studies that the caliber of the deep venous system in these subject is diminished.[30] As the attenuated deep venous system results in smaller thrombi and emboli, the subtlety of PE symptoms can be explained. As pulmonary hypertension is so prevalent, a recurrence of these small PE is inferred.

CAUSE OF PE IN CHRONIC SCI

The cause of PE and its source, DVT, in chronic SCI is attributable to venous stasis in the absence of the calf and pulmonary pumps to return venous blood to the chest. A measure of this deficit is the low cardiac output, which is reduced to 40% of normal in the sitting position.[31,32] However, venous stasis by itself has not been shown to be sufficient to induce venous thrombosis. Other procoagulation factors, such as a serum factor, demonstrated by Wessler *et al.*[33] in animal experiments, may be necessary. Infection has been associated with PE surveys in the able-bodied,[34] and infection is pervasive in the SCI subject. In our recent survey of chronic SCI subjects with PE, the common terminal illness was sepsis.[5] It is suggested that septicemia from any source is an important factor in the genesis of PE in the chronic SCI subject.

CONSEQUENCES OF PE

PE in chronic SCI subjects, apparently recurrent, leads to insidious pulmonary hypertension. Evaluation by transthoracic echocardiography in our survey showed that in some instances the pulmonary hypertension can be severe, reaching systemic levels.[5] Right ventricular hypertrophy and dilatation are the sequellae before a fatal terminal event.[4] The consequences of cor pulmonale are reduced cardiac output

and impaired circulation, which, in the tetraplegic, may compound dyspnea and orthostatic hypotension.[35] Poor circulation also leads to further venous stasis, reduced skin integrity or impaired wound healing.[36]

DIAGNOSIS

The diagnosis of PE in the chronic SCI subject must begin with the realization that first, PE is not rare in this group; second, PE may be minor; third, symptoms may be atypical and fourth, infection may be a precipitating factor. A lower threshold of suspicion is necessary. Once suspected, a review of the current and previous ECGs may reveal a RBBB, which in turn may suggest acute or chronic PE, provided other causes of RBBB such as coronary artery disease and chronic obstructive pulmonary disease are ruled out. Beside RBBB, other ECG pointers to PE are: atrial arrhythmias, right axis deviation in the frontal plane, clockwise rotation in the horizontal plane and the S1Q3T3 pattern. Transthoracic echocardiography can document the severity of pulmonary hypertension and detect the occasional proximal PE in the main pulmonary arteries or the right ventricular outflow tract. Popular compression ultrasonography may demonstrate DVT and heighten suspicion; but one should go directly to a more definitive graphic test. Fortunately, many centers do not have to diagnose PE based on the non-specific abnormalities of the perfusion lung scan or deal with the logistic issues and invasiveness of pulmonary angiography. Computerized tomography with angiography, which has a resolution down to 1 mm,[1] is the procedure of choice.[37]

TREATMENT

Prevention of the subclinical, cumulative PE of chronic SCI may be possible by application of prophylactic measures at the onset of a risk factor, sepsis. Prevention of PE recurrences once PE is diagnosed may be possible with the same measures. However, either primary or secondary preventive treatments are problematic in the chronic SCI subject.

The choice of anticoagulation represents a particular hazard for bleeding in the presence of recent surgically repair of a decubitus ulcer and can delay healing of a medically treated decubitus ulcer,[38] although not contraindicated in sepsis.[34] Furthermore, anticoagulation by itself may not be effective. As summarized in Table 2 heparin alone does not prevent DVT in the acute SCI subject, but is effective in combination with functional electrical stimulation or elastic stockings.[39,40] The effect of elastic stockings alone has not been tested.

A second approach, physical therapy alone, can be considered. There is evidence the range of motion is effective. An older survey for DVT by Todd *et al.*[41] in acute SCI subjects without the now standard a range of motion to the extremities, revealed a high prevalence of DVT; but a later survey in the same setting with range of motion three times daily revealed a marked reduction in DVT, Table 2.[42] Nevertheless, a risk to this prophylaxis can be noted: at least five PE events and two fatal PE events immediately after range of motion or turns in bed in the acute SCI population have been reported.[43,44] These preventive measures, may not be easy or without controversy; however, they deserve consideration and careful application in the individual subject.

Table 2 Prophylaxis of DVT in acute SCI

Author	*Year*	N	*Procedures*	*DVT*	P
Merli[39]	1988	17	No LDH	8	
		16	LDH	8	
		15	LDH+FES	1	
Merli[40]	1992	19	LDH+stockings	1	<0.05
Todd[41]	1976	12	ROM 0–1/day, no LDH	9	
Frisbie[42]	1981	17	ROM 2 per day, no LDH	1	
		16	ROM 2 per day, LDH	1	<0.01

Abbreviations: DVT, deep venous thrombosis; FES, functional electrical stimulation; LDH, low dose heparin (5,000 units subcutaneously twice a day); ROM, range of motion to extremities; SCI, spinal cord injury.
Comparisons were FES or elastic stockings vs neither of these for the studies of Merli *et al.* and ROM 0–1/day vs 2–3 per day for Todd *et al.* *P* represents the confidence that the differences were due to chance–comparisons made by χ^2 testing.

CONCLUSION

The prevalence of PE cannot be as low as previously thought. Although overt PE with a significant mortality is more common in the acute SCI subject, subclinical PE is more prevalent in the chronic SCI subject. Subclinical PE recurrences over a long period of time may result in significant pulmonary hypertension and right ventricular dilatation leading to the occurrence of RBBB on ECG. As the clinical picture may be atypical, non-specific or even misleading, a need exists for the SCI physician to lower the threshold for the diagnosis PE in this group and utilize the readily available ECG as a tool to suspect acute or chronic PE in the presence of RBBB or other abnormalities indicative of PE. A transthoracic echocardiogram may be obtained to document pulmonary hypertension. Computerized tomography with angiography may then be used as the most sensitive, accurate tool for the definitive diagnosis of PE. A conservative, longstanding treatment of PE and its recurrence remains to be evaluated in the chronic SCI subject, considering the pros and cons of each therapeutic option based on the clinical situation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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