Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques
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CRD summary
This review concluded that catheter-directed therapy was a relatively safe and effective alternative treatment for acute massive pulmonary embolism. Given that the appropriateness of pooling was unclear and that study quality was not assessed, the authors' conclusions may not be reliable.

Authors' objectives
To investigate the efficacy and safety of modern catheter-directed therapy as an alternative treatment for massive pulmonary embolism.

Searching
MEDLINE and EMBASE were searched for studies in all languages, from January 1990 to September 2008. Search terms were reported. Reference lists of retrieved studies were examined for further studies. Studies available only as abstracts were excluded.

Study selection
Studies of patients with massive pulmonary embolism in haemodynamic shock that reported results of treatment with modern catheter-directed therapy (in at least three consecutive patients) were eligible for inclusion. In studies that included patients without hypotension or that used outdated catheter-directed therapy techniques, data pertaining to hypotensive patients that received modern catheter-directed therapy was included.

Modern catheter-directed therapy was defined as: use of low-profile catheters and devices (10F or less, i.e. 0.33 mm diameter or less); catheter-directed mechanical fragmentation and/or aspiration of emboli using any catheter type, and intra-clot thrombolytic injection if a local drug was infused. Clinical success was defined as stabilisation of haemodynamics, resolution of hypoxia, and survival of a massive pulmonary embolism, as reported in the primary study.

The included studies were performed in a variety of countries in Europe, Asia, South America and in the USA. The mean age of the included patients ranged from 33 to 68 years. The majority of included patients did not receive systemic thrombolytic therapy and were treated with catheter-directed therapy as the first adjunct to heparin anticoagulation. Catheter-directed therapy was initiated by mechanical means alone in one third of patients (where reported). Local thrombolysis used was tissue-type plasminogen activator, tenecteplase, urokinase or streptokinase. The most common mechanical intervention used was rotating pigtail fragmentation of emboli with/without other catheter manoeuvres.

Study selection was performed by more than one reviewer and there were no disagreements.

Assessment of study quality
Methodological quality of the primary studies was not assessed. The studies were graded by study design according to published criteria (Strength of Recommendation Taxonomy, SORT).

Data extraction
Percentage clinical success from catheter-directed therapy and 95% confidence intervals (CIs) and complication rates were extracted from each study by two reviewers.

Methods of synthesis
Clinical success rates and complication rates were pooled using fixed-effect and random-effects models. Results of random-effects models were reported due to significant heterogeneity.
Heterogeneity was assessed using the Cochran Q and $I^2$ statistics. $P<0.10$ was considered to indicate significant heterogeneity and $I^2>50\%$ indicated substantial heterogeneity. Unpaired t-tests were used to investigate the sources of heterogeneity (e.g. prospective versus retrospective studies, publication date and sample size).

Publication bias was assessed using a funnel plot. A trim-and-fill method was used to adjust for publication bias.

**Results of the review**
 Thirty-five studies were included in the review ($n=594$ patients; range 3 to 164). Six studies were prospective and 29 were retrospective. All of the studies were uncontrolled.

Catheter-directed therapy was associated with a clinical success rate of 86.5% (95% CI 82.2 to 90.2; 35 studies); there was significant heterogeneity ($Q = 60.6, p=0.004$). Pooled results were similar for prospective versus retrospective study designs, studies published before 2001, and studies with ≤10 patients meeting inclusion criteria. The pooled frequency of success rate was higher in studies in which at least 80% of the patients received thrombolytic therapy during the procedure (91.2%, 95% CI 86.3 to 95.1) and in studies in which at least 80% of the patients received extended local thrombolytic therapy (89.2%, 95% CI 82.8 to 94.3); no significant heterogeneity was detected for either outcome.

Publication bias was suggested by Egger test ($p=0.033$) and funnel plot analyses. The trim-and-fill method revealed that a few smaller studies with much lower success rates may be missing or under reported.

Catheter-directed therapy was associated with a pooled risk of minor procedural complications of 7.9% (95% CI 5.0 to 11.3) and a pooled risk of major procedural complications of 2.4% (95% CI 1.9 to 4.3). Both outcomes were associated with significant heterogeneity (minor complications $Q=123.1, p<0.0001$; major complications $Q=94.0, p<0.0001$).

**Authors' conclusions**
 Catheter-directed therapy was a relatively safe and effective treatment for acute massive pulmonary embolism.

**CRD commentary**
The research question was supported by clear inclusion criteria. Two relevant databases were searched for studies in any language, reducing the risk of language bias. Unpublished studies did not appear to have been sought, increasing the possibility of publication bias. This was supported by the results of tests for publication bias. Study selection and data extraction were performed by two reviewers, which reduced the risk of error and bias within the review.

Study quality was not assessed, so the reliability of the individual studies was unclear. It appeared that the studies may have been quite clinically heterogeneous, so pooling might not have been appropriate. Possible sources of heterogeneity were investigated.

Given that the appropriateness of pooling was unclear and that study quality was not assessed, the authors' conclusions may not be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that the best available evidence indicated that modern catheter-directed therapy should be considered as a first-line treatment option for patients with acute massive pulmonary embolism at centres with appropriate expertise.

**Research:** The authors stated that further prospective studies are needed to confirm the findings of this study and to refine existing catheter-directed therapy protocols. To minimise selection bias, the authors recommended that future studies should enrol consecutive patients with massive pulmonary embolism by applying a standard catheter-directed therapy protocol, and by evaluating outcomes by using well-defined criteria for clinical successes and complications.

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