

Thrombolysis in acute pulmonary embolism

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<http://dx.doi.org/10.1590/1806-9282.66.3.263>

SUMMARY

OBJECTIVES: Acute pulmonary embolism (APE) is an important cause of cardiovascular mortality, due mainly to hemodynamic instability. In these cases, the recommendation is to perform some reperfusion procedure, with systemic thrombolysis being the main therapy used. However, national data evaluating the efficacy and safety of thrombolysis are scarce.

METHODS: Retrospective analysis of a case series. We included 13 patients diagnosed with high-risk APE and 4 patients with intermediate-high risk from a single-center, who were treated with alteplase 100mg.

RESULTS: The mean age of the patients was 55 years, most of them female (76.4%). Among the risk factors for VTE were immobilization (41.17%), contraceptive use (35.29%), cancer (17.63%), and previous history of DVT (11.76%). The most frequent clinical manifestations of APE were dyspnea (88.23%), hypoxia (82.35%), hypotension (82.35%), and tachycardia (64.70%). 82.35% of the patients had echocardiographic signs of right ventricular dysfunction, and 52.94% had increased troponin and BNP. Severe bleeding associated with thrombolysis occurred in 17.54% of cases. No patient died due to bleeding. There were 8 deaths from right ventricular failure (47%), 6 in the cases of patients presenting as high-risk APE (35.3%), and 2 in the cases of intermediate-high risk (11.8%).

CONCLUSION: Thrombolysis in patients with high-risk APE or intermediate-high risk had a severe bleeding rate of 17.6%. However, the high mortality of this population (47%) due to right ventricular failure justifies the use of this therapeutic modality.

KEYWORDS: Pulmonary embolism. Thrombolytic therapy. Tissue plasminogen activator. Ventricular dysfunction, right.

INTRODUCTION

Acute pulmonary embolism (APE) is the third leading cause of death from a cardiovascular cause, behind only acute myocardial infarction and cerebrovascular accidents¹{Fernandes, 2016, New anticoagulants for the treatment of venous thromboembolism}. Although it is an easily preventable and treatable disease, it is estimated that every year, more than 3 million people

die as a result of venous thromboembolism (VTE) and its most severe clinical manifestation, APE²⁻⁴.

The main determinant of APE's clinical outcome is the right ventricle (RV) response to the acute increase of its afterload due to the increased pulmonary vascular resistance induced by the presence of a clot and its induced vasoconstriction^{5,6}. When there is clear

DATE OF SUBMISSION: 26-Aug-2019

DATE OF ACCEPTANCE: 31-Aug-2019

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right-ventricular failure induced by APE with hemodynamic instability and hypotension, the recommendation, as a consensus, is some reperfusion procedure to reduce the afterload sharply and revert RV failure⁷⁻⁹. As a rule, the therapy of choice in these cases is systemic thrombolysis. However, due to the risk of its main adverse event, i.e., bleeding, the use of thrombolytic drugs is still well below the actual clinical need of APE patients with hemodynamic instability¹⁰. Another aggravating factor is that, in the medical literature, there is still scarce safety and efficacy data stating the role of this therapeutic strategy in the clinical management of APE patients at high risk of death, mainly in the national environment.

In certain situations, thrombolytic treatment is also an option for patients with medium-high risk APE. These patients are those who are able to maintain systemic perfusion with adequate systemic arterial pressure at the expense of RV stress. That stress is identified by the presence of abnormal biomarkers (BNP or troponin) RV imaging (via echo with pulmonary hypertension or RV dilation, or even an abnormal RV/LV ratio on a tomography)¹¹. The benefits of using a thrombolytic drug in this situation are more questionable, and there is also no data available in the literature on the clinical outcomes of thrombolysis in this population for our location¹².

In this study, we present a series of 17 cases from a secondary general hospital who were submitted to thrombolytic therapy with alteplase for the treatment of PTE. We evaluated its effectiveness and safety.

METHODS

This is a case-series study, analyzed retrospectively through the review of medical records. The study included 13 patients with a diagnosis of high-risk PTE and four patients of medium-high risk, according to the classification suggested by the consensus of the European Society of Cardiology/European Respiratory Society¹¹, from January 2014 to May 2016, in the General Hospital of Florianópolis - SC, and who were submitted to thrombolytic therapy with alteplase at a dose of 100 mg.

RESULTS

The mean age of patients was 55 years (23 to 84 years). Most patients were female (76.4%). Among the most prevalent risks for VTE, immobilization was present in 41.17%, followed by the use of oral contraception (35.29%). Three patients had a history of cancer (17.63%), demonstrating the relevance of this clinical condition, particularly in our area^{13,14}. Two cases had a history of deep vein thrombosis (11.76%). The epidemiological data of patients with APE are expressed in Figure 1.

The most frequent clinical manifestation of APE was sudden-onset dyspnea (88.23%), followed by O₂ saturation lower than 90%, and systemic hypotension (defined as systolic blood pressure below 100 mmHg (82.35%). Tachycardia and lower levels of consciousness were observed in 11 patients (64.70%), while

FIGURE 1. RISK FACTORS IDENTIFIED IN PATIENTS WITH APE

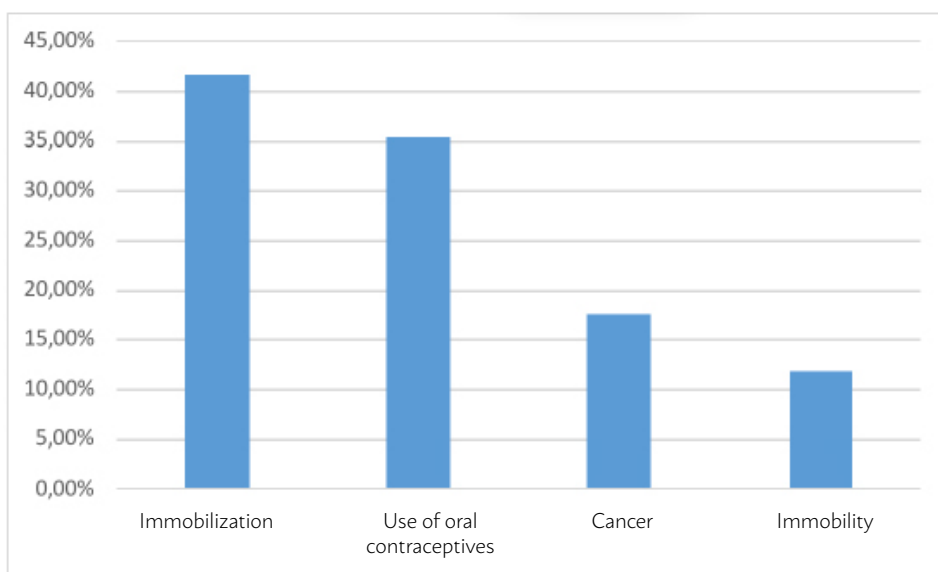
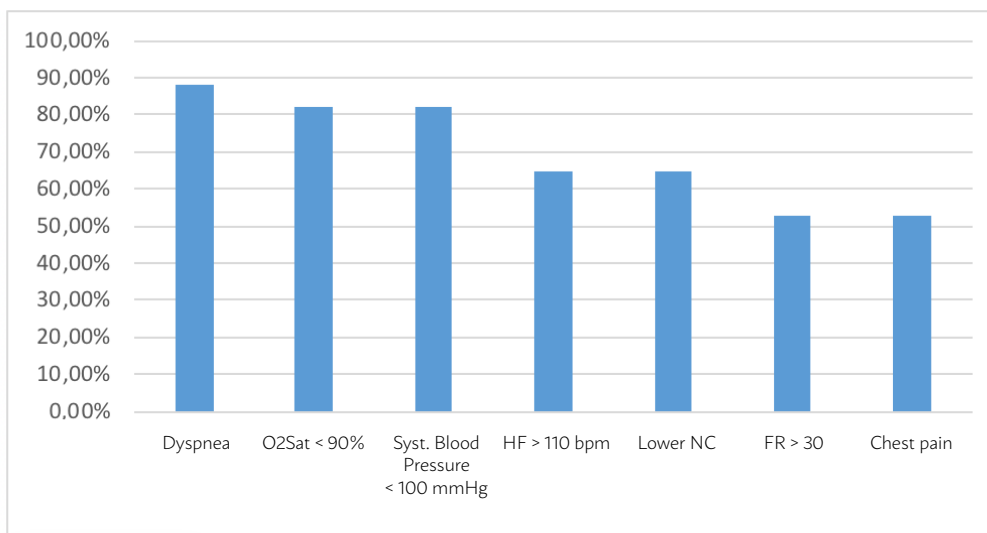
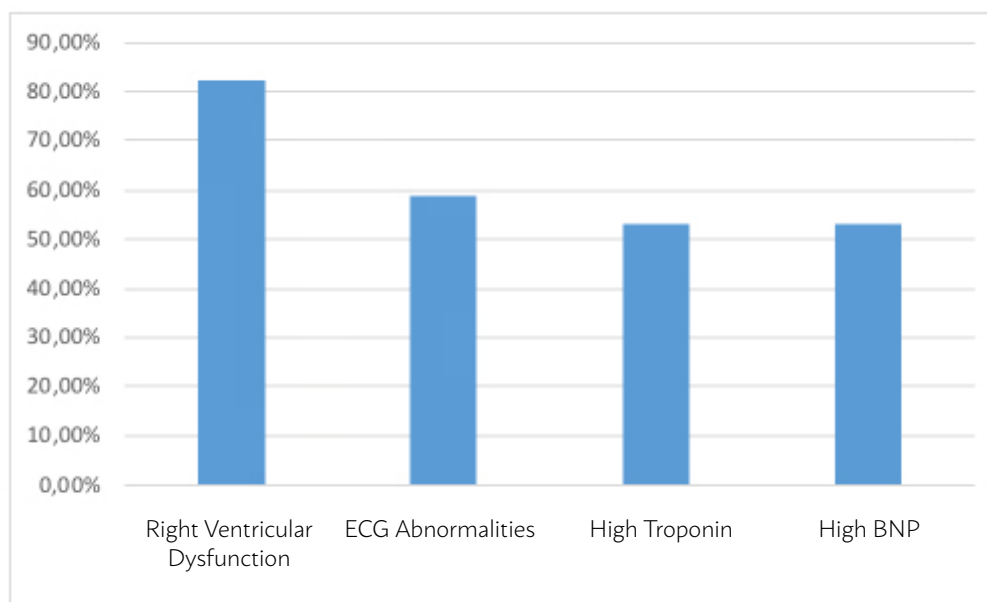


FIGURE 2. MAIN SIGNS AND SYMPTOMS PRESENTED BY APE PATIENTS.**FIGURE 3.** MAIN PROPAEDEUTICS CHANGES PRESENTED BY APE PATIENTS.

tachypnea and chest pain was observed in 52.94% (Figure 2).

Fourteen patients (82.35%) presented echocardiographic signs of right ventricular dysfunction, such as the RV hypokinesis, increased pulmonary artery systolic pressure (PASP), paradoxical septal movement, and dilatation of the right chambers. Electrocardiographic abnormalities were observed in 10 patients (58.82%), with a S1Q3T3 pattern in two cases, sinus tachycardia in one case, and atrial fibrillation in another. Nine cases had increased troponin and brain natriuretic peptide (BNP) values, corresponding to 52.94% (Figure 3)

Severe bleeding associated with thrombolytic therapy occurred in three cases (17.54%). The sites of the

bleeding were retroperitoneal hematoma and hematoma associated with the puncture site of the central venous catheter. No patient died due to bleeding. There were, in total, eight deaths due to right ventricular failure (47%): six among the cases of patients who presented initially as high-risk APE (35.3%) and two among the cases of medium-high risk (11.8%). The data regarding the efficacy and safety of thrombolytic therapy are shown in Table 1

DISCUSSION

The most severe clinical presentation of venous thromboembolic disease is APE with hemodynamic

TABLE 1. EFFICACY AND SAFETY OF THROMBOLYTIC TREATMENT FOR APE

	Efficacy (death due to right ventricular failure)	Safety (greater bleeding)
high-risk APE - systolic BP <90 mmHg (n=13)	6 (35.3%)	3 (17.6%)
Medium-risk high APE - systolic BP >90 mmHg, with RV dysfunction -image plus laboratory testing (n=4)	2 (11.8%)	0

instability. Our study highlights the seriousness of this situation in the national context (47% mortality) and demonstrates that the use of thrombolytic therapy is a viable alternative, with a quite acceptable rate of adverse events (greater bleeding in 17.6% of cases), considering the high lethality of the clinical situation. Data evaluating the efficacy and safety of thrombolytic treatment in Brasil are extremely rare. To our knowledge, this is the first time a series of cases reporting this treatment in the Brazilian context of APE is published.

Thrombolysis is the treatment of choice for high-risk APE, recommended by the most recent international consensus¹¹. However, its main adverse event, i.e., severe bleeding, is an inhibiting factor to its use in patients with a clear indication⁸. Our data demonstrate that, in the national context, although bleeding is, indeed, a condition associated with the use of thrombolytic therapy, its frequency is equivalent to half of the deaths induced by RV dysfunction associated with APE. Thus, the use of thrombolytic drugs in these more difficult situations, with hemodynamic instability and high risk of death, is justified.

For severe patients, considered as of medium-high risk, the role of thrombolysis is less clear. The Peitho study evaluated 1,006 patients in this situation and, despite having identified a benefit from thrombolysis performed with tenecteplase, which reduced the use of intubation or vasoactive drugs, could not identify benefits in terms of mortality. In addition, the use of thrombolytic drugs presented a rate of central nervous system bleeding ten times greater than the conventional treatment with conventional anticoagulation (2 vs. 0.2%, $p=0.003$)¹⁵. Systemic thrombolysis also had no impact on the residual dyspnea or the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) after two years¹⁶. Full anticoagulation would be the main treatment for CTEPH prevention¹⁷.

However, our data demonstrated that this population, in the national context, presents a high mortality rate and is not considered a candidate for thrombolytic treatment; thus, it must be monitored intensively for early identification of organic dysfunction and tissue hypoperfusion.

Recent national data evaluated different aspects of APE diagnosis and risk stratification in our context. The validation of the Pesi risk score¹⁸, the lack of relevance of the Wells and Geneva scores for the APE diagnosis in patients with clinical comorbidities¹⁹, and the use of magnetic resonance imaging to identify the severity of APE {Pasin, 2017 #7398} demonstrate the relevance of APE in the Brazilian medical literature. However, objective data on the treatment of more severe presentations of APE in the Brazilian context are still not available. Thus, our study aims to bridge part of this gap in science, contributing to the construction of epidemiological data on APE in Brasil.

Our study has a number of limitations. It is an uncontrolled case series from a single center. The indication for thrombolytic therapy was systematical, but at the discretion of the assistant physician. Moreover, we do not have data on APE patients with an indication to receive thrombolytic treatment, but who, for some reason, did not receive it. However, the considerable number of patients included and the scarcity of Brazilian data in the literature justify the analysis and interpretation of our data with due caution.

CONCLUSION

Thrombolytic therapy in this series of 17 cases from a single Brazilian center with high-risk or medium-high risk APE patients presented a rate of severe bleeding of 17.6%. However, the high mortality in this population (47%) due to right ventricular failure justifies the use of this therapy, despite the potential morbidity. No patient died due to bleeding in this series.

Ethical aspects

No conflict of interest have been reported by any author

Contributions of the authors

TSB, MG, and HB were responsible for data acquisition. EPO and CLMD completed the first draft. CJF supervised the study and reviewed the draft and final version.

RESUMO

OBJETIVOS: A embolia pulmonar aguda (EAP) é uma causa importante de mortalidade cardiovascular ao causar instabilidade hemodinâmica. Nesses casos, a recomendação é a realização de algum procedimento de reperfusão, sendo a trombólise sistêmica a principal terapia utilizada. No entanto, dados nacionais avaliando a eficácia e a segurança da trombólise são escassos.

MÉTODO: Análise retrospectiva de uma série de casos. Foram incluídos 13 pacientes com o diagnóstico de EAP de alto risco e quatro pacientes de risco intermediário-alto, de um único centro, e que foram tratados com alteplase 100 mg.

RESULTADOS: A média de idade dos pacientes foi 55 anos, sendo a maioria do gênero feminino (76,4%). Dos fatores de risco para TEV, estavam presentes a imobilização (41,17%), o uso de anticoncepcionais (35,29%), câncer (17,63%) e história prévia de TVP (11,76%). As manifestações clínicas mais frequentes da EAP foram dispnéia (88,23%), hipóxia (82,35%), hipotensão (82,35%) e taquicardia (64,70%); 82,35% dos pacientes apresentaram sinais ecocardiográficos de disfunção ventricular direita e 52,94% apresentaram aumento da troponina e BNP. Sangramento grave associado à trombólise ocorreu em 17,54% dos casos. Nenhum paciente faleceu em decorrência de sangramento. Houve oito mortes por insuficiência ventricular direita (47%): seis nos casos de paciente que se apresentaram como EAP de alto risco (35,3%) e duas nos casos de risco intermediário-alto (11,8%).

CONCLUSÃO: A trombólise nos pacientes com EAP de alto risco ou risco intermediário-alto apresentou uma taxa de sangramento grave de 17,6%. No entanto, a alta mortalidade dessa população (47%) por insuficiência ventricular direita justifica o uso desta modalidade terapêutica.

PALAVRAS-CHAVE: Embolia pulmonar. Terapia trombolítica. Ativador de plasminogênio tecidual. Disfunção ventricular direita.

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