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Right heart ischemia in cases of sepsis

T. Fracasso [a,*], L. Jentgens [b], H. Pfeiffer [b], C. Sauerland [c], P. Mangin [a], A. Schmeling [b]

[a] University Center of Legal Medicine, Lausanne–Geneva, Rue Michel-Servet 1, 1211 Geneva, Switzerland
[b] Institute of Legal Medicine, University Hospital Münster, Röntgenstr. 23, 48149 Münster, Germany
[c] Institute of Biostatistics and Clinical Research, University of Münster, Schmeddingstr. 56, 48129 Münster, Germany

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ABSTRACT

Data from the literature suggest that cases of sepsis complicated by right ventricular (RV) dysfunction have poorer prognosis. In these cases progressive hypoperfusion associated to increasing, injury-related, pulmonary vascular resistance account for RV ischemia. In the present analysis, we wanted to evaluate whether prevalent RV cardiac ischemic damage could be detected in a series of fatal sepsis cases. We retrospectively investigated 20 cases of sepsis that underwent forensic autopsy (study group—11♀, 9♂, mean age 57 years) and compared them to a group of 20 cases of hanging (hanging group—4 ♀, 16 ♂, mean age 44 years) as well as to a group of 20 cases of myocardial infarction (MI group—9 ♀, 11 ♂, mean age 65 years), as examples of cardiac damage due to global hypoxia during agony and ischemic damage, respectively. We performed immunohistochemistry with the antibodies anti-fibronectin and C5b-9. The reactions were semiquantitively classified and the groups were compared. In 30% of the cases of sepsis prevalent RV ischemic damage could be detected with the antibody anti-fibronectin. This expression was significantly different from that observed in cases of MI ($p = 0.028$) and hanging ($p < 0.001$). Our study showed that, in cases of fatal sepsis, prevalent RV ischemic damage occurred in a substantial minority of cases.

1. Introduction

Sepsis is a systemic inflammatory response of the host to the presence of microorganisms characterized by mortality varying between 30 and 90% [1]. Severe sepsis and septic shock are more severe clinical forms of the same illness; in the first, organ hypoperfusion and progressive failure are observed while refractory hypotension is typically observed in the second [2]. Myocardial dysfunction is frequent in case of sepsis: in a prospective study on 106 patients with severe sepsis and septic shock, Pulido et al. observed myocardial dysfunction in 64% and its occurrence was associated to higher mortality [3]. Though left ventricular (LV) or global heart dysfunction are often observed, a special subgroup of patients at higher mortality risk is represented by those developing right ventricular (RV) dysfunction [4]. Besides increasing circulating levels of toxins and cytokines with depressant effect on myocardium, progressive hypoperfusion associated with acute pulmonary injury-related increased vascular resistance account for RV ischemia [2,5].

We have recently developed an immunohistochemical method for the detection of prevalent ischemic damage at RV, determining acute right heart failure and death in cases of severe fat embolism and pulmonary thromboembolism [6,7].

In the present analysis, we wanted to evaluate whether prevalent RV cardiac ischemic damage could be detected in a series of fatal sepsis cases.

2. Material and methods

2.1. Investigated cases

We retrospectively investigated 20 cases of sepsis that underwent forensic autopsy (study group—11♀, 9♂, mean age 57 years). Moreover, a group of 20 cases of hanging (hanging group—4 ♀, 16 ♂, mean age 44 years) as well as a group of 20 cases of myocardial infarction (MI group—9 ♀, 11 ♂, mean age 65 years) were included as examples of cardiac damage due to global hypoxia during agony and ischemic damage, respectively. All cases

* Corresponding author. Tel.: +41 0 22 379 49 07; fax: +41 0 22 372 96 53.
E-mail addresses: Tony.Fracasso@hcuge.ch (T. Fracasso), Heidi.Pfeiffer@ukmuenster.de (H. Pfeiffer), sauerla@uni-muenster.de (C. Sauerland), Patrice.Manging@hcuge.ch (P. Mangin), Andreas.Schmeling@ukmuenster.de (A. Schmeling).

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were investigated at the Institute of Legal Medicine of the University Hospital in Münster, Germany, between 1996 and 2009. In each case, information about the circumstances of death as well as autopsy records was available. In 18 cases included in the study group, sepsis was diagnosed at hospital. In 5 cases the diagnosis in the death certificate was sepsis, in 5 cases septic shock and in 8 cases multiple organ failure in sepsis. In two cases of unexplained death outside a hospital, sepsis was diagnosed postmortem. All cases of myocardial infarction were diagnosed by means of postmortem investigations including histology.

An overview of the investigated cases is given in Tables S1–S3.

2.2. Immunohistochemical reactions

In each case, immunohistochemical reactions with the antibodies fibronectin (Polyclonal Rabbit Anti-Human, DAKO Deutschland GmbH, Hamburg, Germany) and C5b-9 (Monoclonal Mouse Anti-Human, DAKO Deutschland GmbH, Hamburg, Germany) of both cardiac ventricles (free wall of the right ventricle RV, anterior and/or posterior wall of the left ventricle LV) were prepared as described elsewhere [8,9]. A blind investigation of the slides was performed by two different observers with final consensual evaluation. Immunohistochemical reactions were classified into four degrees (0—negative reaction, 1—single cell reaction, 2—group cell reaction and 3—diffuse reaction—Figs. 1 and 2).

2.3. Statistical analysis

The degree of cardiac damage was registered in each case in both ventricles. Moreover a parameter Δ that is the difference between the degree damage at the RV and the LV was calculated in each case.

The degree of damage at both ventricles as well as the parameter Δ was compared between the groups.

Explorative statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

Fisher's exact test was performed for statistical analysis. p-Values were regarded as significant in case $p \leq 0.05$.

2.4. Histological investigations

In the group sepsis, histology slides of the lungs stained with hematoxylin and eosin were revised for lung pathology. Bronchopneumonia was diagnosed when patchy, diffuse, suppurative consolidation foci next to inflamed bronchioles were observed. Acute respiratory distress syndrome (ARDS) was diagnosed in case of evidence of interstitial and alveolar edema with focal intra-alveolar accumulation of neutrophils, macrophages and red blood cells, denuding alveolar epithelium and hyaline membranes in the alveoli [10].

3. Results

Fibronectin was significantly more expressed in LV in case of MI compared to sepsis ($p < 0.01$) and hanging ($p < 0.01$), where the expression was instead similar comparing the study group to hanging. C5b-9 was similarly expressed in LV in MI and sepsis. Its expression was similar to sepsis in the group hanging but significantly lower than in MI ($p < 0.01$).

In RV, fibronectin was more expressed in sepsis than in MI and hanging ($p = 0.028$, $p < 0.001$, respectively). The antibody anti-C5b-9 was similarly expressed in MI and sepsis ($p = 0.84$) and significantly more expressed in sepsis than hanging ($p = 0.02$). These results are summarized in Table 1.

The comparison of the parameter Δ fibronectin showed a statistically different distribution in cases of sepsis compared to MI ($p = 0.0095$) and to cases of hanging ($p = 0.039$). A different distribution was also observed in the comparison between MI and hanging ($p = 0.014$).

The comparison of the parameter Δ C5b-9 showed a similar distribution in cases of sepsis compared to MI ($p = 0.34$). In these groups C5b-9 expression was significantly different in comparison to the group hanging ($p = 0.02$ for both comparisons). These results are summarized in Table 2.

Prevalent RV damage (detected by at least one antibody) was observed in 6 cases in the group sepsis (30%). In the groups MI and hanging, prevalent RV damage was never observed.

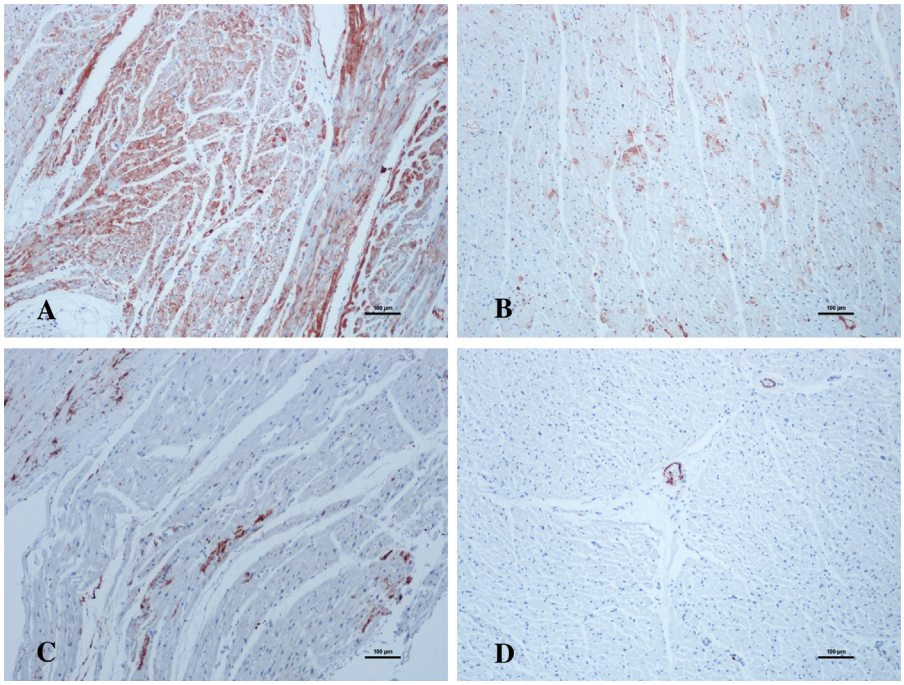

Fig. 1. Example of fibronectin and C5b-9 expression in a cases of sepsis (ID3, TableS1). (A) RV fibronectin, degree 3. (B) LV fibronectin, degree 2. (C) RV C5b-9, degree 2. (D) LV fibronectin, degree 0. Magnification ×100.