

CLINICAL SCIENCE

Postmortem diagnosis of acute myocardial infarction in patients with acute respiratory failure - demographics, etiologic and pulmonary histologic analysis

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OBJECTIVES: Acute respiratory failure is present in 5% of patients with acute myocardial infarction and is responsible for 20% to 30% of the fatal post-acute myocardial infarction. The role of inflammation associated with pulmonary edema as a cause of acute respiratory failure post-acute myocardial infarction remains to be determined. We aimed to describe the demographics, etiologic data and histological pulmonary findings obtained through autopsies of patients who died during the period from 1990 to 2008 due to acute respiratory failure with no diagnosis of acute myocardial infarction during life.

METHODS: This study considers 4,223 autopsies of patients who died of acute respiratory failure that was not preceded by any particular diagnosis while they were alive. The diagnosis of acute myocardial infarction was given in 218 (4.63%) patients. The age, sex and major associated diseases were recorded for each patient. Pulmonary histopathology was categorized as follows: diffuse alveolar damage, pulmonary edema, alveolar hemorrhage and lymphoplasmacytic interstitial pneumonia. The odds ratio of acute myocardial infarction associated with specific histopathology was determined by logistic regression.

RESULTS: In total, 147 men were included in the study. The mean age at the time of death was 64 years. Pulmonary histopathology revealed pulmonary edema as well as the presence of diffuse alveolar damage in 72.9% of patients. Bacterial bronchopneumonia was present in 11.9% of patients, systemic arterial hypertension in 10.1% and dilated cardiomyopathy in 6.9%. A multivariate analysis demonstrated a significant positive association between acute myocardial infarction with diffuse alveolar damage and pulmonary edema.

CONCLUSIONS: For the first time, we demonstrated that in autopsies of patients with acute respiratory failure as the cause of death, 5% were diagnosed with acute myocardial infarction. Pulmonary histology revealed a significant inflammatory response, which has not previously been reported.

KEYWORDS: Inflammation; Respiratory failure; Acute myocardial infarction.

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INTRODUCTION

Acute respiratory failure (ARF) is a major cause of death in patients with a variety of primary underlying diseases (1-4). The clinical and radiographic findings of ARF are nonspecific (5-7). Prompt investigation and diagnosis are essential to improving patient survival (8-10). The complexity of clinical presentations makes diagnosis a constant challenge for the clinician (8-10).

It is well known that acute myocardial infarction (AMI) could be present as ARF in approximately 17% of patients and is associated with poor short- and long-term prognoses (11-15). Intrahospital and 1-year mortality have been observed, respectively, in approximately 17% and 35% of cases (11,16). The prompt and correct diagnosis of AMI in patients with a nonspecific presentation of ARF in the emergency department may improve survival (13,16,17). The role of inflammation in ARF after AMI has been studied and may be as important as elevated pressures (17). No report thus far has described pulmonary findings related to possible inflammation in such patients.

In this context, we performed a retrospective study of 4,710 autopsies in patients with ARF as the cause of death who were not diagnosed with an AMI during life to better describe the demographics, etiological data and associated histological pulmonary findings and diseases.

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No potential conflict of interest was reported.

METHODS

Autopsies

The present study was performed at a tertiary healthcare center. From 1990 to 2008, 26,560 medical autopsies were performed (annual mean of 1,889 autopsies). We considered 4,710 (17.7%) patients for whom ARF was the cause of death without any specific related diagnosis while the patient was alive. The diagnosis of AMI was made in 218 (4.63%) cases. Histological pulmonary analysis was performed in 210 cases of AMI. For eight (3.67%) patients, the histological pulmonary findings could not be reviewed because the pulmonary tissue was not available. In this study, we reviewed all available microscopic and macroscopic diagnoses made during the autopsy as well as the medical records of each patient.

The diagnosis of ARF was made based on the clinical description and/or death certificate and defined as a $\text{PaO}_2 < 60$ mmHg or $\text{PaCO}_2 > 50$ mmHg with $\text{pH} < 7.30$ while breathing room air (1-3). We excluded patients younger than one year of age because of the possibility of congenital heart diseases and hyaline membrane disease. Individuals who were not diagnosed with ARF and AMI were also excluded.

Cases of healed myocardial infarction were not included. We only considered AMI. The macroscopic diagnosis of AMI was considered mainly during the examination of transverse ventricular sections. The initial modifications became more evident after 12 and 24 hours. The ischemic area could easily be observed (approximately 2 to 6 hours after AMI) with a nitroblue tetrazolium (NBT) enzymatic reaction or with triphenyltetrazolium chloride (TTC). The exact period of evolution is very difficult to determine, but these two methods allowed us to identify patients who died between 2 hours and 7 days after a myocardial infarction. Microscopic analyses were started approximately 3 to 12 hours after death with coagulate necrosis and vacuolar degeneration. Neutrophil infiltration was more intense between the second and sixth day. Granulation tissue became more evident after the second week.

We also obtained data regarding each patient's age, sex and major underlying associated diseases (as determined at the time of autopsy).

The clinical data from patients enrolled in the study were collected with legal permission after informed consent was obtained from a family member and after the approval of the Internal Review Board was obtained.

After a complete review, pulmonary pathological reports were categorized as follows:

- Diffuse alveolar damage (DAD): diffuse involvement and the uniform temporal appearance of alveolar collapse, hyaline membranes, obliterative fibrosis, neosepta formation and moderately organizing fibrosis.
- Pulmonary edema (PE): the accumulation of proteinaceous fluid in the alveolar spaces, giving rise to the appearance of a granular, pink coagulate within these spaces.
- Alveolar hemorrhage (AH): the presence of blood in the alveolar spaces.
- Lymphoplasmacytic interstitial pneumonia (LPIP): widened and edematous alveolar septa, usually accompanied by mononuclear inflammatory infiltrates

composed of lymphocytes, histiocytes, plasma cells and neutrophils.

All lungs were analyzed by microscopy, even when medical records indicated the patient's diagnosis. For at least four weeks, the lungs were fixed in 10% formalin prepared in 0.9% saline. We studied a minimum of five sections per lung (total ten sections per person), regardless of the presence or absence of morphologically demonstrable lesions. Paraffin-embedded tissue sections were assessed following hematoxylin and eosin staining. To document the presence and distribution of the wide spectrum of infectious agents to which this population is susceptible, we prepared a variety of special stains (Periodic acid-Schiff test, immunohistochemistry analysis, fluorescence, Ziehl-Neelsen, Gram, Mucicarmine and Gomori's methenamine silver stain) for selected tissue sections. Bacterial bronchopneumonia (BBP) was defined as the presence of cell consolidation with polymorphonuclear leukocyte accumulation in bronchioles and adjacent alveoli. For the diagnosis of cytomegalovirus and fungal pneumonia, histological evidence of lung involvement with or without tissue culture was required. Severe sepsis and/or septic shock were defined as sepsis in addition to organ dysfunction or a clinical diagnosis of arterial hypotension, which may or may not result in aggressive fluid resuscitation. Diagnoses of *Mycobacterium tuberculosis* infection and atypical mycobacterial infection were confirmed using fluorescence and Ziehl-Neelsen techniques as well as Lowenstein-Jensen cultures. The proportion method and biochemistry were used for the identification of all positive cultures.

Dilated cardiomyopathy refers to all causes of cardiac insufficiency associated with dilation of the left ventricle chamber, not only the idiopathic form. Hypertrophic cardiomyopathy refers only to cases of genetic disturbance and not to all cases of ventricular wall thickening.

Statistical analysis

A descriptive analysis of the data included the median, minimum and maximum values. The probability (odds ratio) that patients would develop specific histopathological pulmonary patterns or die of ARF-related pulmonary alterations was determined by logistic regression. The variables included the following major diseases and/or comorbidities that were found: BBP, systemic arterial hypertension, dilated cardiomyopathy, pulmonary embolism, hypertrophic cardiomyopathy, chronic obstructive pulmonary disease, diabetes mellitus, sepsis and/or septic shock and brain stroke. All of the statistical procedures were performed using SPSS v10.0 statistical software. Statistical significance was set at 5% (*p*-value).

RESULTS

In total, 218 autopsies (4.63%) of patients with ARF who died between 1990 and 2008 were not diagnosed with an AMI while they were still alive. The patients' ages ranged from 16 to 90 years (median of 64). A total of 147 (67.4%) men and 71 (32.6%) women were included in the study. The demographic data are listed in Table 1.

We observed a single associated disease other than AMI in 46 (21.1%) cases, two diseases in 16 (7.3%), three in 16 (7.3%) and four in 8 (3.7%) cases. In 132 (60.6%) patients, AMI was the only cause of death.

Table 1 - Demographic data for autopsied patients with ARF and AMI.

Age groups (years)	Sex		Total
	Male	Female	
1 to 50	28	17	45 (20.6%)
51 to 80	106	45	151 (69.3%)
> 80	13	9	22 (10.1%)
Total	147	71	218

A total of 158 diseases and/or comorbidities other than AMI were observed. The major diagnoses in patients with ARF and AMI are shown in Table 2. BBP was present in 11.9% of patients (26 cases) and was the most frequent pulmonary complication found at the time of autopsy. Systemic arterial hypertension was the second most frequent complication and was observed in 10.1% of patients (22 cases), followed by dilated cardiomyopathy in 6.9% (15), pulmonary embolism in 6.0% (13), hypertrophic cardiomyopathy in 4.6% (10), chronic obstructive pulmonary disease in 3.7% (8), diabetes mellitus in 3.7% (8), sepsis and/or septic shock in 3.2% (7) and stroke in 2.8% (6). Other diagnoses with minor prevalence accounted for 27.2% of diseases.

The pulmonary histopathological analysis showed PE in 72.9% (159) of patients, DAD in 17.4% (38), LPIP in 4.1% (9) and AH in 1.8% (4).

The multivariate analysis showing the significant associations between AMI and different histopathological findings is presented in Table 3.

DISCUSSION

The accurate early treatment of ARF remains an important problem in the management of critical patients. Despite recent technological advances in tools for diagnosis, the autopsy has remained an important complementary tool for the identification and understanding of disease. Autopsy studies have revealed important differences between autopsy findings and the clinical diagnosis antemortem (18-25). Such diagnostic disagreement can vary from 10 to 90% depending on the disease and the population involved (5-10,19-21,26-32). Perkins et al. (19) showed that among the patients who died in the intensive care unit, 39% of the cases had major missed diagnoses. AMI was the main missed diagnosis and was present in approximately 10% of the cases. In almost every studied patient with AMI, the clinical diagnosis premortem was

Table 2 - Major diagnoses in patients with ARF and AMI.

Associated diseases	Number (% of cases)
BBP	26 (11.9)
Systemic arterial hypertension	22 (10.1)
Dilated cardiomyopathy	15 (6.9)
Pulmonary embolism	13 (6.0)
Hypertrophic cardiomyopathy	10 (4.6)
COPD	8 (3.7)
Diabetes mellitus	8 (3.7)
Sepsis and/or septic shock	7 (3.2)
Stroke	6 (2.8)

*BBP = bacterial bronchopneumonia; COPD = chronic obstructive pulmonary disease.

BCP (19). These discrepancies might be attributable to different clinical manifestations of a single disease and to poor-quality medical care (5).

In the present study, we observed a prevalence of AMI nondiagnosis of approximately 5% among patients with ARF. Others authors have reported similar data (19,22). A comparison between clinical and autopsy diagnoses in a cardiology hospital published in 2007 reported that approximately 5% of deaths were not diagnosed with AMI. The concordance rate between autopsy and premortem diagnoses of AMI was 71%; among 67% of these cases, the AMI was only subendocardial (22).

Most analyzed patients were males (67%), and the mean age was 64 years. The occurrence of ischemic equivalents such as dyspnea is frequent among female and older patients (17). The majority of studies showed a median age between 69 and 80 years among patients with PE after AMI (11-16). Nevertheless, we observed that most of those diagnosed were males but that they were not older patients, as expected, perhaps because of an association with ARF and death in all cases, which was not considered in other studies. Flutowski et al. (16) reported a median age of 70 years among patients with PE after AMI. Women accounted for 54% of cases (16).

In 132 (60.6%) patients, AMI was the only cause of death as revealed by autopsy. Many diseases and/or comorbidities [158] other than AMI were observed in patients with ARF. BBP was present in 11.9% of patients and was the most frequent pulmonary complication found at the time of autopsy, followed by systemic arterial hypertension (10.1%). Among patients with ARF, BBP is often the initial cause of pulmonary disease, but BBP sometimes appears as a complication of other pathologies, mainly in immunocompromised and intubated patients (33-36).

Dilated cardiomyopathy, pulmonary embolism, hypertrophic cardiomyopathy, chronic obstructive pulmonary disease, diabetes mellitus, sepsis and/or septic shock and brain stroke were also present in many cases. The prevalence (39.4% of cases) of more than one diagnosis demonstrates the complexity and severity of illness among the patients that presented ARF as the cause of death after AMI. These findings could indicate the necessity of a different therapeutic strategy for these patients with poor prognoses (4,13,19,21-24). A study published in 2008 analyzed the use of continuous positive airway pressure in patients with PE secondary to AMI and reported an intrahospital mortality of 11%. The authors reported that all patients who died had associated diagnoses, such as severe sepsis, BBP, stroke and pulmonary embolism. These findings are similar to our results (12).

As expected, PE was the most common pattern observed (72.9% of cases) and was also the most specific finding associated with AMI, as described previously in other studies (4,16,17). AMI has been described as the most important etiologic factor associated with the development of PE in hospitalized patients (16). AMI is the most frequent cause of heart failure and PE mainly due to the consequent elevation of the left ventricular diastolic, venous and pulmonary capillary pressure. This redistributes fluid from the pulmonary capillaries to the interstitial and alveolar space (16,17).

Interestingly, DAD was also associated with AMI. This trend has not been reported for patients with AMI. This indicates that an inflammatory response could present as an

Table 3 - Multivariate analysis with the statistical association between AMI and various histopathological findings.

	DAD			PE			AH			LPIP		
	OR	p-value**	CI 95%	OR	p-value**	CI 95%	OR	p-value**	CI 95%	OR	p-value**	CI 95%
IAM	3.14	<0.001	2.18 – 4.54	6.19	<0.001	4.50 – 8.52	5.67	0.001	2.08 – 15.44	4.94	NS	0.71 – 6.32

ARF after AMI, as suggested by other authors (11,17,37-40). Normally, DAD is associated with an intense inflammatory response, which is sometimes related to the cause of death and may be associated with an extended AMI. There is an emerging interest in the role of inflammatory mediators in AMI. Myocardial injury is in part the result of activation of the inflammatory system, which involves the production and release of proinflammatory cytokines, activation of the complement system, the production of autoantibodies, the overexpression of major histocompatibility complex molecules, and the expression of adhesion molecules that may perpetuate the inflammatory state (40). In this context, the cytokines studied most often in the context of heart failure are tumor necrosis factor and interleukin-6. Other molecules such as C-reactive protein, selectins and endothelin-1 are also related to PE (11,37,40). Some studies have suggested that interleukin-6 mediates endothelial activation in pulmonary vessels (11). Endothelin-1 could increase vascular permeability by inducing the production of leukocyte adhesion molecules and the consequent activation of neutrophils, which would amplify the inflammatory response in the lungs (38). Therefore, larger investigational studies are needed for a better understanding of inflammatory cytokine activation in the lung after AMI. This knowledge may play a role in improving patient outcomes through early diagnosis, timely prevention, and therapeutic intervention. The use of anti-inflammatory agents in AMI should be reconsidered, mainly in patients with ARF (40).

AH was also associated with AMI. Nevertheless, we think that the association with AMI is not as relevant because of the small number of patients (4 cases).

Further studies are necessary to elucidate the complete pulmonary physiopathological mechanism involved in AMI and the development of ARF.

Limitations

First and foremost, this was a retrospective study of medical reports, for which the quality of information can be limited. The second limitation of our study is related to interobserver variability, even taking into account that, at our institution, all autopsies were performed by the resident pathologist under the supervision of a senior pathologist, who also checks the histological analysis to prepare the final reports. Different opinions can be held by different observers. In addition, the accuracy of autopsy findings also depends on the interest and skill of the pathologist.

AUTHOR CONTRIBUTIONS

Soeiro AM was the major investigator, responsible for data collection, writing and data analysis. Ruppert AD contributed to data collection, writing and data analysis. Almeida MCF contributed to writing and data analysis. Canzian M contributed to the histopathological pulmonary analysis. Capelozzi VL contributed to the histopathological pulmonary analysis and was the major investigator. Serrano Jr. CV was the major investigator.

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