The potential value of histological analysis of thrombi extracted through mechanical thrombectomy during acute ischemic stroke treatment

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Abramat

Studies on thrombus composition in acute stroke or acute myocardial infarction may help elucidate clot etiology and understand reperfusion success or failure. Moreover, such studies may certainly aid in the development of new technologies aimed at retrieving specific subtypes of thrombi; as a matter of fact, thrombus composition is suggested to influence the choice of techniques used during mechanical thrombectomy and plays a role in potential device and thrombus interaction. Over the years, histological analysis on the composition of thrombi causing ischemic stroke has proved to be a powerful tool to set standard prevention and treatment protocols. By isolating clot components, it is possible to provide a more accurate diagnosis and distinguish different stroke subtypes. Studies on histological clot composition support the theory that cryptogenic stroke can have a cardiogenic origin too. Components found in thrombi extracted from stroke patients support the importance of antithrombotic therapy in preventing and treating cerebral ischemia; however, more studies are needed to improve results in all types and subtypes of stroke. Hence, more research is required to further comprehend the role that platelets, fibrin, von Willebrand factor (vWF), and DNA play in relation to mechanical thrombectomy and recombinant tissue plasminogen activator (rtPA) resistance and to overcome certain limitations. (Anatol J Cardiol 2020; 23: 254-9)

Keywords: thrombus, composition, ischemic stroke, thrombectomy, thrombolysis, recombinant tissue plasminogen activator

Introduction

Myocardial infarction is the leading cause of death in high-or middle-income countries and the second most relevant cause of disability worldwide (1), while stroke is the second cause of death worldwide and the second leading cause of disability in Western countries (2). For decades, percutaneous coronary intervention has been the gold standard for the treatment and prevention of acute myocardial infarction, and although its combined use with thrombus extraction is a matter of discussion among experts, it has surely opened new doors in terms of research. Extracted thrombi are stained, analyzed, and employed to support new advancements in the diagnosis, treatment, prevention, and prognosis of myocardial infarctions. Furthermore, thrombus extraction devices were introduced for the treatment of acute ischemic stroke many years later, and from 2004 onward most Western countries began to include this technique in the standard care of acute cerebral ischemia (3). Stent retrievers not only represented an improvement in the clinical outcome of stroke therapy, but also inspired research in finding new answers to questions that most certainly would have been left unanswered. Treatment of mechanical thrombectomy in acute ischemic stroke aimed to reperfuse cerebral tissue and minimize neurological damage (4). Similarly to histological and immunohistochemical analyses on thrombi retrieved from coronary arteries, stroke research has supported clarifications in terms of diagnosis, prevention, prognosis, and treatment throughout the past decade, by utilizing specimens retrieved from the cerebral circulation. Many studies focused on stroke and myocardial infarctions have concluded that analyzing thrombus composition can provide insights into their etiology and predict successful reperfusion following intravenous thrombolysis and mechanical thrombectomy. Moreover, such studies may certainly assist in the development of new technologies aimed at retrieving...
specific subtypes of thrombi. In fact, thrombus composition is suggested to influence the choice of techniques used during mechanical thrombectomy and plays a role in potential device and clot interaction (5). Here, we review the importance of histological and immunohistochemical analyses of thrombi extracted during mechanical thrombectomy in the diagnosis, prevention, and treatment of acute ischemic stroke.

Etiology of stroke according to composition

The etiology of ischemic stroke can also be studied through the composition of retrieved thrombi. A better understanding of thrombus origin is a powerful tool for prevention, treatment, and prognosis of ischemic stroke. Stroke subtypes are classified into 5 categories based on etiology, using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification: (1) large artery atherosclerosis (LAA), (2) small vessel occlusion (SVO), (3) cardioembolism (CE), (4) stroke of other determined etiology, and (5) stroke of undetermined etiology (5). A newer system called ASCOD (A for atherosclerosis, S for small vessel disease, C for cardiac pathology, and D for other causes) to categorize ischemic stroke patients was introduced in 2009. This system distinguishes patient in more detail the differences between diseases underlying a cerebral ischemic event in a stroke patient. The Oxford classification only considers size and location of cerebral infarction, whereas TOAST and CCS classifications involve the disease directly related to ischemic stroke, neglecting underlying causes. ASCOD, proposed in 2013, introduces a fifth element – “D” for dissection – and similarly to the ASCO classification, three degrees of causality between the index ischemic stroke and each category are mentioned. Certainly, the biggest difference and one of the main advantages of the ASCOD system is the lack of definitions such as “undetermined,” “cryptogenic,” or “embolic stroke of unknown source.” These categories are too difficult to define and may bring discomfort to patients when such definitions differ from one specialist to another. For example, in the event where no ASCOD 1 category is found, specific diseases (grades 2 or 3) can be mentioned, and these diseases can be clinically addressed according to guidelines to reduce recurrence even if a causal relationship between these diseases and ischemic stroke cannot be established yet (Table 1). Grade 1 defines diseases that can potentially be a cause. Grades 2 and 3 are those that have an uncertain and unlikely causal link, respectively. Grade 0 is assigned when no disease is found, whereas grade 9 occurs if there is no sufficient data to grade a disease (6). Atherosclerosis of large vessels (aortic arch, internal carotid artery, vertebral artery, and stems of the main arteries of Willis’ circle) constitutes approximately 25% of all causes of acute cerebral ischemia. Small vessel disease accounts for about 25% of all causes of cerebral ischemia and lacunar infarcts. Despite appearing as small lesions (<15 mm on CT and <20 mm on MRI), small vessel disease is associated with severe neurological deficit and poor clinical outcome. CE is known to cause approximately 25% of all strokes, with atrial fibrillation being the trigger in 90% of cases. Thrombi in the left atrium and ventricle are additional high-risk causes, whereas atrial septum abnormalities, including the patent foramen ovale, are considered low risk or “unclear” depending on individual cases. In the remaining 25% of causes, the trigger remains unclear despite extensive diagnostic tests, and thus, these are classified as cryptogenic. In younger patients, more than 70% of cases are cryptogenic. However, there is increasingly higher evidence to also have a vast cardiac origin for the cryptogenic subtypes, and recently, the concept of embolic stroke of undetermined source (ESUS) was introduced as a cryptogenic stroke subgroup. For the majority of patients with ESUS, undetected paroxysmal atrial fibrillation is considered as the cause. Common causes are present in approximately 70%-75% of all ischemic strokes (7). Thrombi can be sampled, stored in formalin, embedded in paraffin, and subsequently cut into slices ranging between 3 and 10 µm. Staining methods can involve basic histological proce-

| Table 1. TOAST and ASCOD classification systems |
|-----------------------------------------------|
| **TOAST**                                      | **ASCOD**                                    |
| **Subtypes**                                   | Atherosclerosis                              |
| Large artery atherosclerosis                   | Cardioembolism                               |
| Cardioembolism                                | Small vessel disease                         |
| Small vessel disease                          | Dissection                                   |
| Other determined                              | Other                                        |
| Undetermined                                  |                                              |
| **Characteristics**                           | Classification based on stroke mechanisms    |
| Most widely used worldwide                    | Phenotypic classification system             |
| **Advantages**                                | Takes into consideration noncausative factors|
| Accurate prediction of prognosis              |                                              |
| Convenient                                    |                                              |
| Simpler                                       |                                              |
| **Disadvantages**                             | More intricate for interpretation            |
| Large pool of strokes of undetermined origin   | Large number of subtypes                     |
| Less reliable in specific subtypes            |                                              |
Histological analysis of stroke thrombi

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...different from noncardioembolic thrombi, supporting the fact that similar patterns to cardioembolic thrombi, which is clearly differen...t...rocytes located and entrapped in the center and large amounts of fibrin/platelets. Thus, cryptogenic thrombi demonstrate very similar patterns to cardioembolic thrombi, which is clearly different from noncardioembolic thrombi, supporting the fact that...
composition compared with fragments retrieved in passes 3 to 6. These notions may be a useful consideration in determining the treatment strategy as a case evolves and may be useful for the development of new devices to increase rates of 1-pass recanalization (14). Treatment is focused on fast and efficient removal of the occluding thrombus, either via intravenous thrombolysis or via endovascular thrombectomy. However, recanalization is not always successful and factors contributing to failure are not completely understood. Bright field and fluorescence microscopy is used to histologically analyze thrombi retrieved from stroke patients for fibrin, RBCs, von Willebrand factor (vWF), platelets, leukocytes, and DNA. This would show how thrombi are composed of two main types of zones: RBC-rich and platelet-rich areas. RBC-rich areas are characterized by limited complexity because they consist of RBC trapped in a meshwork of fibrin, whereas platelet-rich areas consist of dense structures of fibrin, vWF, and a great amount of leukocytes and DNA. These findings are important to better understand why platelet-rich thrombi tend to be more resistant to thrombolysis and more complicated to retrieve through thrombectomy. It is clear since recently that there is a consistent presence of leukocytes in stroke thrombi, and other than their presence, not much is known about their specific cellular or molecular distribution. Notably, when staining for RBC-rich and platelet-rich areas, leukocytes are primarily found at the interface between RBC-rich and platelet-rich areas. Leukocytes are also consistently present within platelet-rich zones and do not seem to be found generally in RBC-rich areas, which are homogenously spread throughout the erythrocytes. Leukocytes have also been shown to induce thrombus formation by means of extracellular DNA traps. When Feulgen stain is performed on thrombi, large extracellular DNA networks, appearing as extracellular smears, can be seen throughout the majority of retrieved specimens. Relevant amounts of extracellular DNA are observed particularly in platelet-rich areas and boundary zones between platelet-rich and RBC-rich regions, whereas no DNA is found within the RBC-rich regions. Currently, in many Western countries, recombinant tissue plasminogen activator (rtPA) is the only approved medication for thrombolysis in patients with cerebral ischemia, but it is effective in less than half of the patients. For this reason, it is practical to assume the reality of the so-called “rtPA resistance,” even if the mechanisms of actions are not completely understood. RBC-rich thrombi generally respond better to rtPA rather than platelet-rich thrombi. It is safe to state that by inducing fibrin degradation, rtPA can have a direct and efficient thrombolytic effect on RBC-dominant areas, with thin fibrin as the main extracellular skeleton. Platelet-dominant thrombi contain denser fibrin scaffolds mixed with high amounts of other components such as vWF and extracellular DNA. For this reason, it is possible to assume that fibrin, vWF, and DNA form the structural basis of platelet-rich thrombi and that vWF and DNA could characterize the so-called rtPA resistance. Extracellular DNA and histones have indeed been shown to modify the structure of fibrin, making it more resistant to degradation. Leukocytes, more specifically neutrophils, may support thrombosis through the formation of neutrophil extracellular traps. Furthermore, ex vivo studies have demonstrated how rtPA in combination with DNase-1 can be more effective. vWF is associated with thrombus formation by interacting with fibrin in platelet-rich regions. In vitro studies demonstrate how fibrin and vWF interact with each other through factor XIII or by means of thrombin-dependent incorporation, enhancing thrombus formation. Histological results on vWF and fibrin clarify that fibrin degradation with only plasmin is not enough to obtain thrombolysis of platelet-dominant thrombi. By adding the vWF-cleaving enzyme ADAMTS13, it may be possible to target vWF present in thrombi, thus improving the effectiveness of thrombolysis in rtPA-resistant thrombi. This is very similar to the use of DNase-1 in combination with rtPA to tackle extracellular DNA. Recent studies indicate that erythrocyte-rich thrombi are more easily extracted through endovascular procedures compared with more complex fibrin-/platelet-rich thrombi (15, 16). Current retriever devices and available techniques are more efficient with fresher thrombi; however, mechanisms that render platelet-rich thrombi more resistant to interventional procedures are not completely understood. Platelet-dominant thrombi from ischemic stroke patients include dense fibrin/vWF structures, leukocytes, and DNA. These aforementioned thick fibrin fibers trigger higher thrombus rigidity and affect the coefficient of friction and level of physical compression (17). In addition, extracellular DNA is believed to strengthen fibrin structure, making it more resistant to mechanical forces. As a matter of fact, recently a direct proportion between the amount of neutrophil extracellular DNA traps and the number of device passes needed to achieve successful recanalization has been found (18, 19).

Limitations of histopathological analysis of thrombi
After a careful reading of the current literature on the composition of thrombi retrieved from the cerebral vasculature, a few limitations were found that require significant attention. Ischemic strokes treated with mechanical thrombectomy represent only a percentage of total cases, and in all studies the only available thrombi were obtained from those patients in whom the clot did not dissolve spontaneously or during thrombolysis treatment and in whom the thrombus could be successfully retrieved. Most studies present a relatively small patient population size; thus some comparisons are not possible with small sample sizes. Furthermore, the variation in procedural techniques and the combination of devices applied to retrieve the thrombus fragments is a confounding factor that may potentially affect the rates of composition and histological distribution of the components. Another important limitation in many studies is that the use of intravenous rtPA might have already altered the specimens and manipulation with catheters might have produced some thrombi or fragmented them. The retrieved thrombus fragment does not always reflect the whole occlusive thrombus; thus a certain bias toward more stable clot components is common.
Moreover, given the broad variation of clot composition in the evaluated sections of individual specimens, quantitative component assignments may not always be perfectly representative of the entire clot volume. Another important limitation, other than the limited number of case studies, is the predominance of specific types of ischemic stroke. As a matter of fact, most retrieved specimens are extracted from the middle cerebral arteries, rendering the results of a study a mere generalization for all the less represented subtypes. Certain studies involve the use of only hematoxylin and eosin stains for the quantitative analysis, which surely permits a direct comparison of the different components without the risk of methodological differences. However, important components such as platelets and fibrin may not be quantified successfully, and quantification can be subjected to bigger human and statistical error due to difficulties in reaching a consensus. Moreover, the use of immunological techniques may instead improve precision, meanwhile involving greater costs and requiring better equipped laboratories (Table 2).

Conclusion

Over the years, histological analysis aimed to study the composition of thrombi causing ischemic stroke has proved to be a powerful tool to set standard prevention and treatment protocols. By isolating the clot components, it is possible to provide a more accurate diagnosis and distinguish different stroke subtypes. Studies on histological clot composition support the theory that cryptogenic stroke can have a cardiogenic origin too. Components found in thrombi extracted from stroke patients confirm the importance of antithrombotic therapy in preventing and treating cerebral ischemia, but more studies are needed to improve results for all types and subtypes of stroke. In conclusion, more research and investigations are definitely required to further comprehend the role platelets, fibrin, vWF, and DNA play in relation to mechanical thrombectomy and recombinant rtPA resistance and to overcome the limitations faced by existing literature.

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Table 2. Limitations of studies and possible solutions

| Limitation | Main bias | Potential mitigations |
|------------|-----------|----------------------|
| Small patient population size | Sampling bias | Increase population size |
| Predominance of specific types of ischemic stroke (MCA) | Faulty generalization | Cooperation with other centers (stroke units) |
| Mechanical thrombectomy-treated stroke represent only a percentage of total cases | Exclusion bias | Include patients treated only with intravenous thrombolysis when possible |
| Variation in procedural techniques for retrieval | Confounding bias | Apply categories according to the device used |
| Combination of devices applied for retrieval | Confounding bias | Distinguish and compare specimens in which patients were subjected to intravenous thrombolysis |
| Already altered specimens by intravenous rtPA | Confounding bias | Count and minimize where possible per-pass retrieval of specimens |
| Manipulation with catheters | | |
| Retrieved thrombus material not always reflects the whole occlusive thrombus | Survivorship bias | Minimize need for more stable thrombi for the purpose of the study |
| Exclusive use of hematoxylin and eosin stains | Observer bias | A large pool of expert raters |
| Immunological procedures | Funding bias | Strengthen inter-rater reliability score |
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