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● *Review*

QUANTITATIVE MEASUREMENT OF ERYTHROCYTE AGGREGATION AS A SYSTEMIC INFLAMMATORY MARKER BY ULTRASOUND IMAGING: A SYSTEMATIC REVIEW

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Abstract—This systematic review is aimed at answering two questions: (i) Is erythrocyte aggregation a useful biomarker in assessing systemic inflammation? (ii) Does quantitative ultrasound imaging provide the non-invasive option to measure erythrocyte aggregation in real time? The search was executed through bibliographic electronic databases CINAHL, EMB Review, EMBASE, MEDLINE, PubMed and the grey literature. The majority of studies correlated elevated erythrocyte aggregation with inflammatory blood markers for several pathologic states. Some studies used "erythrocyte aggregation" as an established marker of systemic inflammation. There were limited but promising articles regarding the use of quantitative ultrasound spectroscopy to monitor erythrocyte aggregation. Similarly, there were limited studies that used other ultrasound techniques to measure systemic inflammation. The quantitative measurement of erythrocyte aggregation has the potential to be a routine clinical marker of inflammation as it can reflect the cumulative inflammatory dynamics *in vivo*, is relatively simple to measure, is cost-effective and has a rapid turnaround time. Technologies like quantitative ultrasound spectroscopy that can measure erythrocyte aggregation non-invasively and in real time may offer the advantage of continuous monitoring of the inflammation state and, thus, may help in rapid decision making in a critical care setup. (E-mail: guy.cloutier@umontreal.ca)

Key Words: **Quantitative ultrasound imaging, Ultrasound spectroscopy, Critical care medicine, Point-of-care monitoring system, Erythrocyte aggregation, Inflammation, Backscatter coefficient, Structure factor.**

INTRODUCTION

Systemic inflammation is a condition associated with several metabolic disorders (Hotamisligil 2006), such as obesity, diabetes, cardiovascular diseases, pre-eclampsia (Schiessl 2007), rheumatoid arthritis (Choy and Panayi 2001), Alzheimer disease (Akiyama et al. 2000), Parkinson disease (McGeer and McGeer 2004), cancers (Mantovani 2005), chronic obstructive pulmonary diseases (Yamamoto et al. 1997) and other critical states, for example, traumatic brain injury (Ramlackhansingh et al. 2011), multiple organ failure (Goris et al. 1985) and cardiac surgery (Asimakopoulos 2001). The systemic inflammatory response syndrome (SIRS), with or without infection, is common in critically ill patients (Gustot 2011). The inflammatory cascade generated after a trauma has been considered a pathophysiologic basis of SIRS. Systemic inflammation is associated with physiologic deterioration and organ dysfunction in such patients (Muckart and Bhagwanjee 1997). It may affect multiple organs (in 10%–15% of cases) leading to poor patient outcomes and increased mortality, particularly in cases of intense vasoplegia (Maharaj and Laffey 2004). A mortality rate

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of 41% was reported in the 10% to 15% of patients experiencing SIRS and multiple organ dysfunction (Warltier et al. 2002). However, the contribution of the inflammatory response to adverse patient outcomes is potentially reversible. Thus, the continuous quantitative measurement of inflammatory markers may offer an advantage for the management of critically ill patients (Urbach et al. 2004).

The continuous monitoring of inflammatory markers in the critical care setup, nonetheless, comes with its own challenges. More than 80 blood markers of inflammation (cytokines and chemokines, immune-related effectors, reactive oxygen and nitrogen species, acute phase proteins, prostaglandins and cyclooxygenase-related factors, mediators such as transcription factors and growth factors and procalcitonin) have been identified in the scientific literature (Brenner et al. 2014; Zakynthinos and Pappa 2009). The information provided by these biomarkers does not necessarily overlap (Ikonomidis et al. 2008), and thus, a single measurement of an inflammatory marker does not reflect the overall dynamics of the inflammation process *in vivo* (Leng et al. 2008; Libby et al. 2002). Moreover, comparisons of cytokine levels are often problematic for the clinician owing to the use of several different techniques to derive them (Leng et al. 2008). Levels of cytokines measured also depend on a number of preanalytical factors such as the blood sample processing and storage, feeding cycle of the patient, anticoagulants used and circadian patterns (Thavasu et al. 1992; Zhou et al. 2010), further complicating the interpretation process.

Undoubtedly, the measurement of several markers over a period through state-of-the-art technologies would provide a better picture of the inflammatory process. Intracellular staining of cytokines utilising fluorescence-activated flow cytometry (Freer and Rindi 2013), multiplex arrays based on flow cytometry, chemiluminescence or electrochemiluminescence have all been used as advanced methods, but these approaches require costly initial setup and highly trained staff (Leng et al. 2008). Rather than the cost and availability of the technology, the main concern, however, in the context of critical care, would be the turnaround time, which ranges from hours to days even with advanced techniques (Leng et al. 2008). These biochemical markers are then of no value when frequent monitoring and rapid medical decisions are required in the intensive care unit. Therefore, despite the valuable clinical information that can be obtained from many inflammatory markers, they have not been used effectively in critical care because of the unavailability of rapid and reliable tests that can be serially determined and could report the overall status of systemic inflammation generated *in vivo*.

We are thus in dire need of such a biomarker that has the potential to report the cumulative quantification of these inflammatory molecules reliably, is relatively simple to measure, is cost effective and has a rapid turnaround time. The quantitative measurement of erythrocyte aggregation could be the one valuable test to monitor the generalized inflammatory process detectable in the blood. In this context, the present systematic review aimed to find out if erythrocyte aggregation can be used as a marker to measure systemic inflammation. Moreover, our review also aimed to determine if non-invasive techniques such as ultrasound can be used to quantitatively measure erythrocyte aggregation *in vivo* in real time, so that it could be used in a critical care setup to serially assess systemic inflammation.

METHODS

The search was executed by an academic librarian (D.Z.) through bibliographic electronic databases CINAHL (from 1937 onwards), EMB Review (from 1991 onwards), EMBASE (from 1974 onwards), MEDLINE (from 1946 onwards), PubMed and the grey literature (CADTH, Clinical Trials, National Guideline Clearing House, National Institute for Health and Care Excellence [NICE], MedNar, Google Scholar and Open Grey). The search combined words and expressions for two conceptual groups: *erythrocyte aggregation* and *inflammation*. To obtain the ultrasonography aspect, we added terms and expressions combined with OR in the second conceptual group (inflammation). We used words and expressions from controlled vocabulary (MeSH, EMTREE and others) and free-text searching. Exact key words used for search in each database are given in Appendix 1. Retained articles had received institutional animal or human ethical committee approvals.

RESULTS

Results of literature search

The initial search through CINAHL, EMB Review, EMBASE, MEDLINE, PubMed and the grey literature identified 1996 references after removing duplicates. Of 1996, 298 were not considered because they were not written in English. One thousand four hundred three articles were not specific to our objectives and thus were excluded after reading the abstract. Further, 98 papers were not retained after careful reading of the full text because of the following reasons: (i) they described erythrocyte aggregation in the context of technical issues in measurements, nitric oxide metabolism, redox balance, anemia, use of biomedical devices and hemostatic agents, presence in several pathologic states, and storage and blood banking, without taking into account inflammation or inflammatory markers directly; (2) they described ultrasound in the context of blood coagulation and blood echogenicity without considering erythrocyte aggregation; and (3) they studied