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Paul Harrison and Alison H Goodall

In this issue we highlight a very topical and timely review by Noris and colleagues entitled "New roles for MPV measurement in clinical practice?" [1], and discuss our newly proposed editorial policy for the minimum requirements for future manuscripts that include MPV measurement as their major focus.

Fast, precise and reliable measurement of platelet number and size was revolutionized in the 1970s by the widespread availability of automated full blood counters that utilise the aperture impedance or "Coulter" principle that was invented 20 years earlier [2]. As a consequence MPV became an additional parameter of interest to both clinicians and researchers and is routinely available on most modern analysers. One of the fascinating aspects of the normal platelet volume distribution is the classical log-normal distribution demonstrating the heterogeneity of platelet size [3]. This also led to the discovery of the inverse relationship between platelet count and MPV that seems to maintain a remarkably tight control on the total platelet mass between individuals. Having defined normality it soon then became apparent that changes in MPV are associated with both acquired and inherited forms of thrombocytopenia. Noris et al discuss how abnormalities in platelet size using MPV are indeed useful for studying and differentiating between inherited forms of macrothrombocytopenia and giant platelet syndromes from other inherited conditions, and from acquired thrombocytopenias [1,4].

However, as they point out, the majority of manuscripts on MPV (1313 papers in Pubmed since 2013; 98 papers which have appeared in this journal since 2006) have focused on the association of MPV with many other clinical conditions such as ischaemic and thrombotic disorders, and their associated clinical outcomes [1]. Many studies have now shown that MPV is raised in patients with thrombosis and can often predict poor outcomes. Norris et al have highlighted a number of important questions. Firstly they question whether a raised MPV is the possible cause of thrombosis or a consequence of the condition, for while there is sound evidence that MPV is influenced by genetic polymorphisms [5], and lifestyle factors [6], these effects account for <20% of natural variation [5,6,7], MPV is also increased following platelet consumption and acceleration of platelet turnover in thrombotic conditions. Noris et al emphasize that the majority of studies were performed during the acute phase of thrombosis which makes these mechanisms highly credible. We would also add that inflammatory mediators, such as IL-6, that are often raised in acute or chronic conditions, may also feedback to the bone marrow, resulting in changes to the whole Megakaryocytic/Platelet axis, polyploidization and consequent thrombopoiesis with a shift towards a more prothrombotic phenotype and a higher MPV [8].

Despite these caveats, Noris et al have highlighted a number of population studies that indeed suggest a potential association between MPV and disease. An editorial by Lippi has also recently stated that "It is now undeniable that the assessment of platelet size should be regarded as a valuable tool for diagnosis and therapeutic monitoring of a wide spectrum of arterial and venous

disorders" [7]. However, interpretation of these studies still requires a note of caution when we also take into consideration the importance of pre-analytical and analytical variables. The dynamic range of MPV is narrow and, outside of macrothrombocytopenia, observed differences between groups are small and the affected groups typically have MPVs that are within the normal range. Noris et al point out that such small differences between patients and controls could be easily masked by the variation due to inadequate standardization of measurements. Pre-analytical variables, such as the anticoagulant used, and the time between blood collection and measurement are known to significantly affect MPV measurements. Although EDTA is traditionally used and recommended for samples destined for blood counting it is well known that platelets collected into EDTA anticoagulants undergo time-dependent platelet swelling and activation [9]. It is therefore critical that in studies where EDTA is the anticoagulant the time delay between sampling and analysis is standardized in both the controls and test samples so that accurate comparisons can be made both within and between studies [10]. Alternative anticoagulants should also be considered; citrate or magnesium sulphate, in an attempt to minimise time-dependent swelling [11]. Even after controlling pre-analytical variables there are also significant differences in MPV values produced by different full blood counters; especially between those from different manufacturers [12]. All current manufacturers apart from Bayer use impedance technology to determine MPV. Although It is well known that impedance measurements perform well in both internal and external quality control (QC) schemes, there are currently no suitable QC materials available to determine both within and between instrument comparisons and long term performance of MPV measurements (Sam Machin, personal communication). It is therefore vital that any study comparing different patient groups utilises the same conditions and technology to measure platelet MPV and counts. This still makes inter-study comparisons difficult when different technologies have been used. Although we agree that clinical utility of MPV indeed has much potential beyond thrombocytopenia, for the measurement to be routinely adopted, standardization and guidelines are urgently required; indeed the International Council for Standardization in Haematology (ICSH) and International Society of Haemostasis and Thrombosis (ISTH) Platelet Physiology Scientific and Standardization Committee (SSC) are currently working towards this goal [13,14]. Future guidelines and recommendations would no doubt help with improving MPV measurements. The future availability of standards with known MPV values would be of enormous value to the field and would not only help to determine both within and between instrument variation but provide more confidence in the reliability of MPV measurements (Sam Machin, personal communication).

The journal Platelets receives large numbers of manuscripts whose primary focus is MPV as a parameter to compare different groups of subjects; probably because as it is an easy, cheap and rapid measurement that is often routinely recorded in clinical data. Although many of these studies have been performed well, and demonstrate an understanding of the limitations of this measure, many do not address these issues sufficiently. We are therefore proposing some minimal requirements for publication in Platelets of any manuscripts focussed on the association of MPV with any disease or condition.

- Firstly, as with any clinical investigation, the study should be adequately powered with evidence of how the power calculations have been determined.

- Comparisons between groups should ideally be matched for age and gender and where this is not possible the data should be analysed for the effects of these demographic variables and adjusted appropriately.
- All blood samples should be collected, handled and processed in the same way so that the effect of pre-analytical variables between the groups is minimised.
- Pre-analytical variables including anticoagulation, accuracy of tube filling and mixing, temperature and time delays between sampling and analysis must also be clearly stated. Ideally the time delay should be standardized but if not the range of times should be limited and stated in the manuscript.
- A full description of the technology used (manufacturer, instrument model, method principle etc), Internal and External Quality control procedures employed and ideally the coefficient of variation of MPV measurement (within and between assays) should be included.

A recent article by Beyan & Beyan [15] that has reviewed 181 recent publications in which MPV measurements have been compared between groups of patients and controls has highlighted how many published articles lack many of these details. For example 47.5% of studies failed to report the time between blood collection and measurement, and 16% of studies did not report either the time of measurement or the instrument used.

In an effort to improve the quality of future manuscripts published in Platelets we require authors submitting articles focussed on MPV as a primary measure to differentiate groups of subjects to address these issues. We agree with Noris et al that the narrow dynamic range of MPV values results in a limited role in either diagnosing or predicting outcomes in any acquired condition, making the need for careful study design, standardised (or at least controlled) measurement, full reporting of how the data were acquired, and appropriate statistical considerations essential requirements for the interpretation of this platelet parameter. We also agree that measurements should perhaps no longer be limited to count and MPV and, were possible, reports should include measurements of immaturity index, other inflammatory markers and a reliable marker of platelet activation if research in this area is to progress.

Declaration of Interest

The authors have no relevant conflict of interest to disclose

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