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Peripheral Blood Monocyte Subset Assessment in Non–ST-Segment Elevation Myocardial Infarction Is Required

We read with great interest both the research paper by Tsujioka et al. (1) and the editorial comment by Shantsila and Lip (2) outlining the role of monocytes in myocardial infarction (MI). We agree that understanding the role of different monocyte population subsets during acute coronary syndromes (ACS) might provide important clinical information; however, much more work is required, and there is a need to express some cautionary notes. An important limitation in the paper by Tsujioka et al. (1) and others referenced by Shantsila and Lip's editorial (2) in considering the kinetics of monocyte chemoattractant protein (MCP)-1 release (3) are the small sample sizes (n = 36 and n = 23 for MI, respectively). Thus, interpretation must be restrained. Our data from 216 patients with ACS do not support the association of the early release kinetics of MCP-1 (the ligand for chemokine [C-C motif] receptor 2 [CCR-2]). Thus, the idea that it is related to the "prompt up-regulation of CCR-2 expressing CD14+CD16- monocytes" might not be correct (2). In our larger ACS population, we found no time-dependent increase in MCP-1 measurement during the first 12 h after the onset of symptoms (4). In addition, Tsujioka et al. (1) present data indicating that there was an increase in the $CD14^{+}CD16^{+}$ subgroup (these cells lack CCR-2; refer to Figs. 3B and 4D in Tsujioka et al. [1]) in that at admission the levels were lower in the MI group as compared with the stable angina group, with subsequent peak levels in the MI group significantly higher (1). However, this cell subpopulation did not correlate with myocardial salvage (1). Moreover, the data are from patients with ST-segment myocardial infarction (STEMI), which tend to be larger infarctions. Data in a more diverse group, including those with smaller events diagnosed with cardiac troponin—which is recommended by the guidelines groups (5)—would be important to see whether differences exist between those groups (1).

If monocyte subgroups are important in non-STEMI, they might prove extremely useful in deciding on the timing of invasive intervention. Non-STEMI patients benefit from early intervention but not necessarily immediate intervention (6). Perhaps data related to monocyte activity and expression would help to differentiate those who might benefit immediately from those who can wait for some hours. Such considerations will require detailed information on the effects of invasive interventions on monocyte subgroups as well as whether serial monitoring is required for risk stratification. These are important issues, which when addressed will shed additional light on the role of monocytes and their laboratory use in risk stratification for patients presenting with ACS.

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Reply

We are grateful to Drs. Kavsak and Jaffe for their valuable comments and suggestions to our study (1). They pose a question regarding the kinetics of monocyte chemoattractant protein (MCP)-1 release. They found no time-dependent increase in MCP-1 measurement during the first 12 h after the onset of symptoms in 216 patients with acute coronary syndromes (2). On the contrary, Matsumori et al. (3) have

demonstrated that plasma MCP-1 levels in 23 patients with acute myocardial infarction (MI) increase as early as 3 h after the onset of chest pain and reach their maximum at 24 h, with further gradual decline. We have no idea about the MCP-1 kinetics, because we did not examine the measurement of circulating MCP-1 in this study (1). Further studies will be needed on this important subject. In addition, in contrast to a previous experimental study (4)—which shows that Ly-6C^{lo} ($CD14^+CD16^+$ analogs) monocytes were found to be critical for myocardial healing via myofibroblasts accumulation, angiogenesis, and deposition of collagen—this study (1) did not show any significant effect of $CD14^+CD16^+$ monocytes on myocardial salvage followed by reperfused MI. However, we could not exclude the possibility that it might potentially be the result of a short period of observation (7 days after reperfusion).

We completely agree with Drs. Kavsak and and Jaffe's supposition that data in a more diverse group, including those with smaller events diagnosed with cardiac troponin, would be important to see whether difference exist between those groups. We also agree with their idea that data about monocyte subgroups would possibly determine the optical timing of intervention in patients with MI without ST-segment elevation (5). Well-designed prospective trials would highlight the effect of circulating distinct monocyte subsets on the optimal timing of intervention in patients for non–ST-segment elevation MI.

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Reply

We thank Drs. Kavsak and Jaffe for their discussion regarding the paper by Tsujioka et al. (1) and our accompanying editorial (2), and we agree that the role of monocytes in the pathogenesis of acute coronary syndromes (ACS) includes a lot of undiscovered areas. Although the significance of high monocyte count for the development of atherothrombotic events and unfavorable course of the recovery from them has been uniformly demonstrated, some controversy still exists in relation to the precise mechanisms responsible for monocyte recruitment to the damaged myocardium in general and monocyte chemoattractant protein (MCP)-1 in particular (3,4).

In addition to a small study by Matsumori et al. (5), other experimental and clinical studies support significant up-regulation of MCP-1 in ACS (as recently reviewed) (6). In the largest of such studies, the OPUS–TIMI (Orbofiban in Patients with Unstable coronary Syndromes–Thrombolysis In Myocardial Infarction) 16 trial (5), MCP-1 was significantly increased in 2,270 patients with ACS compared with stable subjects and was an independent prognostic factor for adverse outcomes (7).

Although the study by Kavsak et al. (8) on 216 patients with ACS did not reveal significant dynamics in MCP-1 at early stages of ACS, this work was limited by only 2 time-points included in the analysis (i.e., admission within 6 h after the onset of symptoms, and at 3 to 12 h later [median 6.5 h]), whereas monocytes are known to peak at 48 to 72 h after ACS onset. Additionally, the study did not include a stable control group and thus might not provide the basis to challenge the hypothesis that "prompt up-regulation of CCR-2 expressing CD14+CD16- monocytes" (2).

In fact, a critical role of MCP-1 for mobilization of monocytes from bone marrow and their homing to the sites of damage has been repeatedly shown. In contrast, mechanisms of recruitment of CD16+ monocyte population are less established. These cells can differentiate from CD16- monocytes or might be formed directly in bone marrow (9). Indeed, their biological role in human cardiac pathology is only scarcely analyzed. The many observations reported by Tsujioka et al. (1) (e.g., reduction of CD16+ monocytes in ACS patients at admission) do not have a robust explanation at present, thus raising further questions for future research. We agree with Drs. Kavsak and Jaffe that "data in a more diverse group" of ACS patients on the dynamics of monocyte subsets are needed to shed further light on their clinical implications.

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