Relationship between mean platelet volume and mitral annular calcification

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Mitral annular calcification (MAC) is associated with several cardiovascular disorders including coronary artery disease (CAD), atherosclerosis, heart failure, and stroke. MAC and atherosclerosis share similar clinical risk factors for cardiovascular diseases, including age, obesity, hypertension, hyperlipidemia, and diabetes mellitus. The aim of this study was to assess the mean platelet volume (MPV), an indicator of platelet activation in patients with MAC. The study group consisted of 101 patients with MAC. An age, sex, and BMI matched control group was composed of 55 patients who were admitted to the echocardiography laboratory due to suspicion of organic heart disease and eventually found to be free of MAC. We measured platelet indices values in patients and controls. MPV was significantly higher in patients with MAC than in controls (8.9 ± 0.8 versus 8.0 ± 0.9 fl, respectively; $P < 0.001$) and platelet distribution width (PDW) was significantly higher in patients with MAC than in controls (15.8 ± 1.3 versus 15.0 ± 1.3%, respectively; $P < 0.001$). MPV was positively correlated with MAC ($P < 0.001$, $r = 0.47$), atrial fibrillation ($P = 0.01$, $r = 0.19$), left atrial ($P = 0.02$, $r = 0.83$) and negatively correlated with platelet count ($P = 0.01$, $r = -0.20$). MPV [odds ratio (OR) 3.89; 95% confidence interval (CI) 1.97–7.67; $P < 0.0001$], and PDW (OR 2.27; 95% CI 1.45–3.55; $P < 0.0001$) were independently associated with the MAC. We have shown that MPV and PDW were significantly elevated in patients with MAC. MPV was correlated with MAC, atrial fibrillation and left atrial and negatively correlated with platelet count. MPV and PDW were independently associated with MAC. *Blood Coagul Fibrinolysis* 24:189–193 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Mitral annular calcification (MAC) is a chronic, degenerative process of calcium and lipid deposition in the mitral valve ring [1]. MAC is associated with several cardiovascular disorders including coronary artery disease (CAD), carotid and aortic atherosclerosis, heart failure, and stroke [2–7]. MAC has also been shown to be independent predictor of cardiovascular events [8–11]. In generally, MAC has been observed in the presence of significant atherosclerosis [12,13]. This was not surprising, because, MAC and atherosclerosis share similar clinical risk factors for cardiovascular diseases, including age, obesity, hypertension, hyperlipidemia, and diabetes mellitus [14,15].

It is known that increased platelet activation and aggregation is closely related to variety of cardiovascular risk factors and cardiovascular disorders [16,17]. As, MAC is closely associated with the above cardiovascular risk factors and cardiovascular disorders in which platelet activation is present, it is reasonable to speculate that platelet activation can also play a role in pathophysiology of MAC. However, to the best of our knowledge, there is no investigation about platelet functions in patients with MAC. Mean platelet volume (MPV) is a simple and easy method of assessing platelet function [18,19]. In comparison to smaller ones, larger platelets have more granules, aggregate more rapidly with collagen, have higher thromboxane A2 levels and express more glycoprotein Ib and IIb/IIIa receptors [20–22]. The aim of this study was to evaluate the relationship between MAC and platelet indices including MPV.

Patient and methods

The study group consisted of 101 patients with MAC (64 women, 37 men, mean age 73.5 ± 7.8 years). An age, sex, and BMI-matched control group was composed of 55 patients (31 women, 24 men with a mean age 72.6 ± 6.5 years) who were admitted to the echocardiography laboratory due to suspicion of organic heart disease and were eventually found to be free of MAC. Hypertension was considered to be present if the systolic pressure was more than 140 mmHg and/or diastolic pressure was more than 90 mmHg or if the individual was taking antihypertensive medications. Diabetes mellitus was defined as a fasting blood glucose level more than 126 mg/dl or current use of a diet or medication to lower blood glucose. The study was approved by the institutional ethics committee and all patients gave their informed consent.

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Exclusion criteria were history of chronic renal and liver disease, moderate-to-severe mitral and aortic regurgitation, moderate-to-severe mitral and aortic stenosis, malignancy, systemic or pulmonary embolism, chronic hematological diseases, acute or chronic inflammatory disease, autoimmune disease, current use of anticoagulant and a prosthetic valve.

Echocardiography

The M-mode, two-dimensional, and Doppler echocardiographic examinations were obtained by using GE VingMed System FiVe (Norway) to assess left atrial diameter, left ventricular systolic and diastolic dimensions, left ventricular ejection fraction and MAC. Left atrial and ventricular dimensions and left ventricular ejection fraction were measured by M-mode echocardiography in the parasternal long-axis view by using the American Echocardiography Society M-mode technique [23]. MAC was defined as an intense echocardiography-producing structure with highly reflective characteristics that was located at the junction of the atrioventricular groove and the posterior or anterior mitral leaflet on the parasternal long-axis, apical four-chamber or two-chamber, or parasternal short-axis view [9]. The presence of mitral and aortic insufficiency was evaluated by Doppler color flow mapping.

Blood sampling

Blood samples were drawn from the antecubital vein by careful venipuncture in a 21 g sterile syringe without stasis at 08.00–10.00 a.m. after a fasting period of 12 h. Glucose, creatinine, and lipid profiles were determined by standard methods. MPV was measured in a blood sample collected in dipotassium ethylenediaminetetraacetic acid (EDTA) tubes (Vacuette). An automatic blood counter (Beckman-Coulter Co, Miami, Florida, USA) was used for whole blood counts. MPV was measured within an hour after sampling.

Statistical analysis

Data were analyzed with the SPSS software version 10.0 for Windows. Continuous variables from the study groups were reported as mean ± SD, categorical variables as percentages. To compare continuous variables, the Student *t*-test or Mann–Whitney U test were used wherein appropriate. Categorical variables were compared with the χ^2 test. The correlations between MPV and MAC and other clinical and laboratory parameters were performed with Pearson and Spearman correlation analysis. A *P* value less than 0.05 was considered statistically significant. The relationship between increased MPV and MAC was analyzed in a multivariate regression analysis adjusted for factors with *P* value less than 0.05 in Tables 1 and 2 with univariate analysis [(glucose, creatinine, left atrial, ejection fraction, AF, platelet count and platelet distribution width (PDW)]. A *P* value less than 0.05 was considered statistically significant.

Table 1 Clinical features and echocardiographic findings of the patients with MAC and control group

	MAC ($n=101$)	Control ($n=55$)	*P*
Age (years)	73.5 ± 7.8	72.6 ± 6.5	0.46
Sex (M/F)	37/64	24/31	0.39
BMI (kg/m^2)	27.1 ± 4.7	28.2 ± 3.8	0.14
SBP (mmHg)	122.4 ± 14.9	123.2 ± 10.3	0.71
DBP (mmHg)	76.9 ± 8.2	77.2 ± 6.7	0.81
Smoking (%)	23 (23%)	7 (12%)	0.12
Glucose (mg/dl)	109.7 ± 28.2	96.3 ± 13.1	0.001
Creatinine (mg/dl)	1.0 ± 0.3	0.9 ± 0.1	0.03
Total cholesterol (mg/dl)	188.3 ± 32.9	192.0 ± 32.0	0.49
Triglycerides (mg/dl)	143.1 ± 60.8	127.7 ± 32.1	0.08
LDL-cholesterol (mg/dl)	114.0 ± 24.8	112.8 ± 34.4	0.80
HDL-cholesterol (mg/dl)	47.5 ± 11.1	49.3 ± 9.5	0.33
LA (mm)	43.2 ± 6.7	36.7 ± 3.3	<0.001
EF (%)	56.1 ± 13.1	64.6 ± 4.3	<0.001
Atrial fibrillation (%)	38 (38)	2 (4)	<0.001
CAD (%)	22 (22)	10 (18)	0.59
Statin use (%)	32 (32)	10 (18)	0.07
Aniplatelet use (%)	55 (55)	28 (50)	0.67

CAD, coronary artery disease; EF, ejection fraction; HDL-cholesterol, high density lipoprotein cholesterol; LA, left atrial diameter; LDL-cholesterol, low density lipoprotein cholesterol; M/F, male to female; MAC, mitral annular calcification. *P* value is for comparison between control and study population.

Results

Clinical features and echocardiographic findings of the study and control groups were summarized in Table 1. There were no statistically significant differences between the two groups with respect to age, sex, BMI, SBP and DBP, smoking status and levels of total cholesterol, triglyceride, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, hemoglobin, and white blood cell (WBC). There were 23 patients with hypertension in patients with MAC and six patients with hypertension in controls and there was no significant difference between two groups with the χ^2 test ($P=0.07$). Glucose levels were significantly higher in patients with MAC than in controls (109.7 ± 28.2 versus 96.3 ± 13.1 mg/dl, respectively; $P=0.001$). There were 16 patients with diabetes mellitus in patients with MAC and one patient with diabetes mellitus in controls and there was a significant difference between two groups with the χ^2 test ($P=0.007$). Creatinine levels were significantly higher in patients with MAC than in controls (1.0 ± 0.3 versus 0.9 ± 0.1 mg/dl, respectively; $P=0.03$). Left atrial diameter was significantly higher in patients with MAC than in controls (43.2 ± 6.7 versus

Table 2 Comparison of the platelet indices of the patients with MAC and control subjects

	MAC ($n=101$)	Control ($n=55$)	*P* value
WBC ($\times10^3$ mg/dl)	7.6 ± 1.7	7.2 ± 2.3	0.28
Hemoglobin (g/dl)	13.4 ± 1.8	13.9 ± 1.6	0.07
Platelet count ($\times10^9$)	246.3 ± 65.1	282.2 ± 63.6	0.001
PDW (%)	15.8 ± 1.3	15.0 ± 1.3	<0.001
MPV (fl)	8.9 ± 0.8	8.0 ± 0.9	<0.001

MAC, mitral annular calcification; MPV, mean platelet volume; PDW, platelet distribution width; WBC, white blood count. *P* value is for comparison between control and study population.

36.7 ± 3.3 mm, respectively; $P < 0.001$). Mean left ventricular ejection fraction was significantly lower in patients with MAC than in controls (56.1 ± 13.1 versus $64.6 \pm 4.3\%$, respectively; $P < 0.001$). There was more atrial fibrillation in patients with MAC than in controls (38 versus 4%, respectively; $P < 0.001$). Comparison of the platelet indices of the patients with MAC and controls was shown in Table 2. Platelet count was significantly lower in patients with MAC than in controls (246.3 ± 65.1 versus $282.2 \pm 63.6 \times 10^9$, respectively; $P = 0.001$). PDW was significantly higher in patients with MAC than in control subjects (15.8 ± 1.3 versus $15.0 \pm 1.3\%$ respectively; $P < 0.001$). MPV was significantly higher in patients with MAC than in controls (8.9 ± 0.8 versus 8.0 ± 0.9 fl, respectively; $P < 0.001$).

Correlation analysis indicated that MPV was positively correlated with MAC ($P < 0.001$, $r = 0.47$), atrial fibrillation ($P = 0.01$, $r = 0.19$), left atrial ($P = 0.02$, $r = 0.83$), and negatively correlated with platelet count ($P = 0.01$, $r = -0.20$).

In multivariate regression analysis, when adjusted for other related univariate factors (glucose, creatinine, left atrial, ejection fraction, presence of atrial fibrillation) MPV [odds ratio (OR) 3.89; 95% confidence interval (CI) 1.97–7.67; $P < 0.0001$], and PDW (OR 2.27; 95% CI 1.45–3.55; $P < 0.0001$) were independently associated with the MAC.

Discussion

In the present study, we examined platelet indices in patients with MAC. We found that MPV and PDW were significantly higher in patients with MAC. MPV was correlated with MAC, atrial fibrillation and left atrial and negatively correlated with platelet count. MPV and PDW were independently associated with the MAC independent of confounding factors.

MAC is associated with several cardiovascular disorders including CAD, carotid and aortic atherosclerosis, heart failure, stroke [2–7]. Previous studies have shown that age, diabetes mellitus, hypertension, and obesity, which are risk factors for atherosclerotic heart disease, are also risk factors for MAC [14,15]. In our study, we have found higher levels of glucose and creatinine in patients with MAC than in controls and our results are consistent with previous studies from this aspect [14,24]. We have also found higher left atrial diameter, lower ejection fraction and higher incidence of atrial fibrillation in patients with MAC than in controls and our results are consistent with previous studies from also this aspect [6,25–27]. It has been shown that increased platelet activation is closely related to variety of cardiovascular risk factors and cardiovascular disorders [16,17]. To the best of our knowledge there is no study investigating the platelet functions in patients with MAC that has similar risk factors for atherosclerotic heart disease.

MAC is largely thought to be a manifestation of atherosclerotic coronary heart disease. This is mainly due to the fact that the risk factors for MAC have been found to be similar to that of coronary artery disease, sharing a common pathogenesis for atherosclerosis.

One can logically think that several cardiovascular disorders associated with MAC including CAD, carotid and aortic atherosclerosis, heart failure, stroke [2–7] and cardiovascular risk factors associated with MAC like age, diabetes mellitus, hypertension, and obesity may cause platelet activation [2–7,14,15]. In our study, there were increased glucose levels (prediabetes), lower ejection fraction, increased incidence of atrial fibrillation and increased left atrial when compared with control group. Previous studies have shown that MPV was elevated in patients with impaired fasting glucose and atrial fibrillation [28,29]. On the contrary, MPV was elevated independent of these cardiovascular disorders and risk factors in our study.

MPV is a simple and easy method of assessing platelet function [18,19]. Platelets are enucleate cells measuring approximately 1–2 μm in length with an average life span of 8–10 days, which are formed via cytoplasmic fragmentation of bone marrow-derived megakaryocytes. Platelets are heterogeneous in size, density, and reactivity. In comparison to smaller ones, larger platelets have more granules, aggregate more rapidly with collagen, have higher thromboxane A2 level and express more glycoprotein Ib and IIb/IIIa receptors [20–22].

To the best of our knowledge, there is no data about MPV in patients with MAC. There are some proposed mechanisms for increased MPV in MAC. Fox *et al.* [30] reported that inflammatory biomarkers; C-reactive protein, interleukin 6 (IL-6), monocyte chemoattractant protein-1, and soluble intercellular cell adhesion molecule-1 were elevated in participants with valvular calcium. MPV reflects the platelet production rate and stimulation. Platelet size is regulated at the level of the megakaryocyte. Researches reported that cytokines such as IL-3 or IL-6 influence megakaryocyte ploidy and can lead to the production of more reactive and larger platelets [31,32]. So IL-6, which is increased in patients with MAC can also cause an increase in MPV values by stimulating the megakaryocyte ploidy. Inflammation might be one of the causes of increased MPV in patients with MAC. Recently, Sucu *et al.* [33] reported that platelet production indices including MPV and PDW were increased in patients with aortic valve sclerosis. It has been shown that age, diabetes mellitus, hypertension, and increased weight, which are risk factors for atherosclerosis are also risk factors for aortic valve sclerosis [15]. As a result, aortic valve sclerosis has a great similarity to MAC and our results are consistent with this study from this aspect. As a difference from this study, MPV and PDW in our study were independently

associated with the MAC independent of confounding factors.

Platelet volume is mainly determined in the bone marrow. It is supposed that the large platelets are caused by a reduced fragmentation of megakaryocytes. MPV has been shown to inversely correlate with the total platelet count as in our study, which could even suggest the consumption of small platelets and a compensatory production of larger reticulated platelets [17]. In our study, platelet count was significantly lower in patients with MAC than in controls and inversely correlated with MPV as consistent with this study.

The small number of patients was the limitation of the study. Moreover, our analysis was based on a simple baseline determination at single time point that may not reflect the patient status over long periods. MPV increases over time in EDTA-anticoagulated samples, and this increase was shown to be proportional with the time period between sample collection and laboratory analysis [34]. Therefore, whole blood count including MPV was determined in less than 1 h to minimize EDTA-induced platelet swelling.

In conclusion, we have shown that MPV and PDW were significantly elevated in patients with MAC compared with controls. MPV was correlated with MAC, atrial fibrillation and left atrial and negatively correlated with platelet count. MPV and PDW were independently associated with the MAC independent of confounding factors. Elevated MPV values may indicate that patients with MAC have a higher risk of systemic thromboembolism due to increased platelet activation. Further prospective studies are mandatory to establish the pathophysiological and clinical significance of increased MPV in patients with MAC.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Nestico PF, Depace NL, Morganroth J, Kotler MN, Ross J. Mitral annular calcification: clinical, pathophysiology, and echocardiographic review. *Am Heart J* 1984; **107**:989–996.

2 Adler Y, Herz I, Vaturi M, Fusman R, Shohat-Zabarski R, Fink N, *et al.* Mitral annular calcium detected by transthoracic echocardiography is a marker for high prevalence and severity of coronary artery disease in patients undergoing coronary angiography. *Am J Cardiol* 1998; **82**:1183–1186.

3 Aronow WS, Ahn C, Kronzon I. Association of mitral annular calcium and of aortic cuspal calcium with coronary artery disease in older patients. *Am J Cardiol* 1999; **84**:1084–1085.

4 Adler Y, Koren A, Fink N, Tanne D, Fusman R, Assali A, *et al.* Association between mitral annulus calcification and carotid atherosclerotic disease. *Stroke* 1998; **29**:1833–1837.

5 Adler Y, Zabarski RS, Vaturi M, Shapira Y, Ehrlich S, Jortner R, *et al.* Association between mitral annulus calcium and aortic atheroma as detected by transesophageal echocardiography. *Am J Cardiol* 1998; **81**:784–786.

6 Mellino M, Salcedo EE, Lever HM, Vasudevan G, Kramer JR. Echographic-quantified severity of mitral anulus calcification: prognostic correlation to related hemodynamic, valvular, rhythm, and conduction abnormalities. *Am Heart J* 1982; **103**:222–225.

7 Benjamin EJ, Plehn JF, D'Agostino RB, Belanger AJ, Comai K, Fuller DL, *et al.* Mitral annular calcification and the risk of stroke in an elderly cohort. *N Engl J Med* 1992; **327**:374–379.

8 Fox CS, Vasan RS, Parise H, Levy D, O'Donnell CJ, D'Agostino RB, *et al.*, Framingham Heart Study. Mitral annular calcification predicts cardiovascular morbidity and mortality: The Framingham Heart Study. *Circulation* 2003; **107**:1492–1496.

9 Kohsaka S, Jin Z, Rundek T, Boden-Albala B, Homma S, Sacco RL, *et al.* Impact of mitral annular calcification on cardiovascular events in a multiethnic community: the Northern Manhattan Study. *JACC Cardiovasc Imaging* 2008; **1**:617–623.

10 Willens HJ, Chirinos JA, Schob A, Veerani A, Perez AJ, Chakko S. The relation between mitral annular calcification and mortality in patients undergoing diagnostic coronary angiography. *Echocardiography* 2006; **23**:717–722.

11 Potpara TS, Vasiljevic ZM, Vujisic-Tesic BD, Marinkovic JM, Polovina MM, Stepanovic JM, *et al.* Mitral annular calcification predicts cardiovascular morbidity and mortality in middle-aged patients with atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Chest* 2011; **140**:902–910.

12 Adler Y, Fink N, Spector D, Wiser I, Sagie A. Mitral annulus calcification: a window to diffuse atherosclerosis of the vascular system. *Atherosclerosis* 2001; **155**:1–8.

13 Allison MA, Cheung F, Criqui MH, Langer RD, Wright MC. Mitral and aortic annular calcifications are highly associated with systemic calcified atherosclerosis. *Circulation* 2006; **113**:861–866.

14 Aronow WS, Schwartz KS, Koenigsberg M. Correlation of serum lipids, calcium and phosphorus, diabetes mellitus, aortic valve stenosis and history of systemic hypertension with presence or absence of mitral anular calcium in persons older than 62 years in a long-term healthcare facility. *Am J Cardiol* 1987; **59**:381–382.

15 Boon A, Cheriex E, Lodder J, Kessels F. Cardiac valve calcification: characteristics of patients with calcification of the mitral annulus or aortic valve. *Heart* 1997; **78**:472–474.

16 Tsiara S, Elisaf M, Jagroop IA, Mikhailidis DP. Platelets as predictors of vascular risk: is there a practical index of platelet activity? *Clin Appl Thromb Hemost* 2003; **9**:177–190.

17 Vizioli L, Muscari S, Muscari A. The relationship of mean platelet volume with the risk and prognosis of cardiovascular diseases. *Int J Clin Pract* 2009; **63**:1509–1515.

18 Park Y, Schoene N, Haris W. Mean platelet volume as an indicator of platelet activation: methodological issues. *Platelets* 2002; **13**:301–306.

19 Boos CJ, Lip GY. Assessment of mean platelet volume in coronary artery disease: what does it mean? *Thromb Res* 2007; **120**:11–13.

20 Martin JF, Trowbridge EA, Salmon GL, Plumb J. The biological significance of platelet volume: its relationship to bleeding time, platelet thromboxane B2 production and megakaryocyte nuclear DNA concentration. *Thromb Res* 1983; **32**:443–460.

21 Jakubowski JA, Thompson CB, Vaillancourt R, Valeri CR, Deykin D. Arachidonic acid metabolism by platelets of differing size. *Br J Haematol* 1983; **5**:503–511.

22 Giles H, Smith REA, Martin JF. Platelet glycoprotein IIb–IIIa and size are increased in acute myocardial infarction. *Eur J Clin Invest* 1994; **24**:69–72.

23 Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; **58**:1072–1083.

24 Rodriguez CJ, Bartz TM, Longstreth WT Jr, Kizer JR, Barasch E, Lloyd-Jones DM, *et al.* Association of annular calcification and aortic valve sclerosis with brain findings on magnetic resonance imaging in community dwelling older adults: the cardiovascular health study. *J Am Coll Cardiol* 2011; **57**:2172–2180.

25 Ariyarajah V, Apiyasawat S, Barac I, Spodick DH. Is the presence of mitral annular calcification associated with poor left atrial function? *Echocardiography* 2009; **26**:877–884.

26 Labovitz AJ, Nelson JG, Windhorst DM, Kennedy HL, Williams GA. Frequency of mitral valve dysfunction from mitral annular calcium as detected by Doppler echocardiography. *Am J Cardiol* 1985; **55**:133–137.

27 Fox CS, Parise H, Vasan RS, Levy D, O'Donnell CJ, D'Agostino RB, *et al.* Mitral annular calcification is a predictor for incident atrial fibrillation. *Atherosclerosis* 2004; **173**:291–294.

28 Coban E, Bostan F, Ozdogan M. The mean platelet volume in subjects with impaired fasting glucose. *Platelets* 2006; **17**:67–69.

29 Colkesen Y, Acil T, Abayli B, Yigit F, Katircibasi T, Kocum T, *et al.* Mean platelet volume is elevated during paroxysmal atrial fibrillation: a marker of increased platelet activation? *Blood Coagul Fibrinolysis* 2008; **19**:411–414.

30 Fox CS, Guo CY, Larson MG, Vasan RS, Parise H, O'Donnell CJ, *et al.* Relations of inflammation and novel risk factors to valvular calcification. *Am J Cardiol* 2006; **97**:1502–1505.
31 Debili N, Masse JM, Katz A, Guichard J, Breton-Gorius J, Vainchenker W. Effects of the recombinant hematopoietic growth factors interleukin-3, interleukin-6, stem cell factor, and leukemia inhibitory factor on the megakaryocytic differentiation of CD34ş cells. *Blood* 1993; **82**:84–95.
32 Brown AS, Hong Y, de Belder A, Beacon H, Beeso J, Sherwood R, *et al.* Megakaryocyte ploidy and platelet changes in human diabetes and atherosclerosis. *Arterioscler Thromb Vasc Biol* 1997; **17**:802–807.
33 Sucu M, Davutoglu V, Sari I, Ozer O, Aksoy M. Relationship between platelet indices and aortic valve sclerosis. *Clin Appl Thromb Hemost* 2010; **16**:563–567.
34 Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. *Blood Coagul Fibrinolysis* 1996; **7**:157–161.

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