Monocytes in Chronic Heart Failure

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Contributor: Julius Liobikas

A long-term condition known as chronic heart failure (CHF) is an ongoing difficulty of the heart in pumping blood enriched in oxygen and required nutrients around the body's tissues. CHF pathogenesis is associated with various causes, and inflammation is one of the most important factors promoting the condition. In addition, monocytes, a group of cells present in the blood and infiltrating tissues, are known to participate in both pro- and anti-inflammatory processes and thus affect myocardial remodeling over time.

heart failure inflammation monocyte

1. The Distribution of Monocytes in CHF

The roles of monocytes under different CHF conditions are complex and, depending on the different monocyte subset number, may encompass inflammatory processes leading to tissue damage or repair [1][2][3][4][5]. Articles investigating monocyte subset ($CD14^{++}$; $CD16^{-}$, $CD14^{++}$; $CD16^{+}$, $CD14^{+}$; $CD16^{++}$) distribution in CHF patients have been summarized. However, works in which monocyte subsets were classified differently are not analyzed in this paper.

Several studies have demonstrated that Mon1 is the predominant subset in HF (87–48%), followed by the Mon2 (5–44%) and Mon3 subsets (7.1–8.4%) [6][1][5][7][8]. Thus, the data indicate a significant expansion of the Mon2 subset in HF patients when compared to healthy controls (see also **Table 1**). Another study examined CHF patients with idiopathic dilated cardiomyopathy (65% of the investigated population) and ischemic heart disease (the remainder of the population; in total, n = 20) and found a higher total leukocyte count and a higher absolute monocyte count in the CHF group compared to healthy people, with no differences in the monocyte subset ratio (but not the cell count) between healthy and diseased people [5]. However, under ambulatory-treated HF conditions, the Mon1 and Mon2 subsets (50.0 ± 17.2% and 42 ± 17.2%, respectively) outnumbered the Mon3 monocytes (8.1 ± 4.0%) [2]. In contrast, the Mon1 subset significantly prevailed over the other two subsets in healthy people (see **Table 1**). Moreover, the proportion of Mon2 monocytes in HF was clearly increased when compared with the proportion in healthy people. Notably, the ratio of different monocyte subsets in HF varies and may be dependent on different CHF conditions and hemodynamic changes [6][5]. For example, CHFrEF can be associated with an increase in the proportion of the Mon3 subset when compared to healthy people and after acute exercise [9][6][5][8], while the Mon2 subset was found to be the most abundant in stable CHF, where patients were not classified according to LVEF [6].

Table 1. The distribution of monocyte subsets in CHF.

Investigated Person		CHF (IDC (65% of Investigated Population) and ISH)	Healthy	Ambulatory Treated CHF I-IV NYHA Functional Class		CHF I-III NYHA Functional Class, 57% ISH, 43% IDC	Healthy	Stabile CVD where LVEF > 43%	Healthy	Systolic CHF II-IV NYHA Functional Class	Healthy
				Alive	Deceased						
Reference		[5]		[1]		[7]		[6]		[8]	
n		20	15	293	107	30	26	14	13	59	29
Gender F/M		7/13	6/9	80/213	29/78	M	M	5/9	8/5	14/45	14/15
Age		51,2 (9,3)	43,5 (5,0)	66,7 (11,9)	76,9 (9,7)	70,9 (2,1)	69,5 (2,2)	60 (9)	59 11)	58,1 (13,9)	59,7 (6,4)
BMI		26,6 (3,8)	24,2 (2,3)								
Exclusion criteria /Inclusion criteria		Active inflammatory or malignant disease and treatment with immunosuppressive agents /CHF patients		Active inflammatory disease /HF irrespective of etiology (at least 1 HF hospitalization or reduced LVEF)		Inflammatory, cancer, autoimmune diseases, malnutrition /CHF lasting longer than 1 year, clinical stability and the same treatment in the last 3 weeks, LVEF≤45%		ACS or coronary revascularization within the last 6 months, current inflammation within the last 6 months, autoimmune or malignant diseases, dialysis-requiring renal failure /stable CAD (1–3 vessel disease)		Acute heart failure or acute coronary syndrome, or haemodialysis, or known systemic inflammatory disease /LVEF<40%, no recent cardiac decompensation	
Leukocyte count (10^6/mL)		**8.24 (1.82)**	**7.17 (1.60)**			**8.34 (0.62)**	**6.45 (0.26)**	7.0 (4.2–9.4)	6.7 (4.3–15.6)		
Monocytes	% of leukocytes	**7.72 (1.88)**	**6.28 (1.24)**					**5.1 (3.6–10.8)**	**3.7 (3.2–8.0)**		
	Count (cells/µL)	**628 (159)**	**450 (128)**			**629 (61)**	**509 (34)**	**354 (131–452)**	**308 (187–440)**		
Monocyte subsets (% of monocytes)	% Mon1	87.34 (3.54)	88.09 (4.73)	50.4 (16.5)	48.9 (19.08)					**73.5 (1.8)**	**84.3 (1.9)**
	% Mon2	4.74 (2.46)	4.51 (2.05)	41.2 (16.5)	44.0 (18.8)	**12.3 (8.7–14.8)**	**5.9 (4.7–6.9)**				

Moreover, several studies found that increased levels of the Mon2 subset and decreased levels of the Mon 1 subset in CHF patients were related to HF severity, which was defined as a New York Heart Association (NYHA) functional class advancement including a reduction of LVEF [7]. Notably, several studies did not find a correlation between the monocyte subset percentage and NYHA functional class or LVEF [1][8]. In addition, the Mon2 levels directly correlated with the C-reactive protein (CRP, which reflects increased systemic inflammation) level and neutrophil count [7]. Recently, it was also found that the Mon2 count was the highest in CHF patients who died [1]. Older deceased patients were characterized by a worse NYHA functional class and contained a higher amino-

Investigated Person		CHF (IDC (65% of Investigated Population) and ISH) [10][11]	Healthy	Ambulatory Treated CHF I-IV NYHA Functional Class		CHF I-III NYHA Functional Class, 57% ISH, 43% IDC	Healthy	Stabile CVD where LVEF > 43% [1]	Healthy	Systolic CHF II-IV NYHA Functional Class	Healthy
				Alive	Deceased						
Monocyte subsets (cells/L)	% Mon3	7.92 (2.19)	7.39 (3.17)	**8.42 (4.0)**	**7.1 (4.0)**						
	Mon1	**550.3 (143.9)**	**395.2 (107)**	327 (222–435)	363 (227–451)			303 (113–437)	266 (161–412) [1]		
	Mon2	**29.3 (17.1)**	**20.7 (13.5)**	**253 (170–374)**	**303 (186–470)**						
	Mon3	**49.3 (17.3)**	**34.1 (20.9)**	48 (35–71) [1]	44 (27–73)						

The readings with statistically significant differences between the healthy and patient groups are marked in bold. CHF: chronic heart failure, CVD: cardiovascular disease, F: female, M: male, ISH: ischemic heart disease, IDC: idiopathic dilated cardiomyopathy, CAD: coronary artery disease, ACS: acute coronary syndrome.

al class the NT-he more with CHF nen with sults are bset [12]. required ss could lead to longer-term inflammation-related deleterious effects in healthy remote myocardial areas. This observation may explain the worse prognosis among HF patients with increased levels of Mon2 monocytes [1]. Another study [13] also reported a link between the amount of the Mon2 subset and poorer prognosis in acute HF patients.

For the sake of completeness, it is worth mentioning a study that did not find any correlation between the percentage of the Mon2 subset or the number of Mon2 cells/μL and the NYHA functional class, LVEF, or estimated glomerular filtration rate, except for a weak statistically significant inverse correlation between the percentage of Mon2 monocytes and LVEF ($r = -0.14$) in ST-Segment Elevation Myocardial Infarction (STEMI) patients [14].

It was demonstrated that the level of Mon2 subset increased in the first week after STEMI and was associated with worsened outcomes during a 2.5-year follow-up period [14]. These findings are in agreement with the results from another study [15] showing increased levels of Mon2 monocytes in patients with worse CHF. Thus, the Mon2 subset may take part in the healing process after MI since this is the only known subset capable of promoting angiogenesis during the healing process after MI [15]. Moreover, Mon2 was the only subset that increased in patients with stable HF, and the amount further increased under acute HF [16]. Notably, a high Mon2 count was associated with better survival during the study. Therefore, Mon2 monocytes may have potentially protective properties in patients with failing hearts. Mon2 could also be related to acute inflammation. Moreover, it seems that these monocytes are not desirable, and may even be harmful, after the acute phase. Thus, it is important to elucidate what determines an increased Mon2 count after the acute period of disease in some patients and a decrease in others.

Assessment of the monocyte subset distribution according to the different etiologies of HF showed no statistically significant differences when percentages of subsets were considered [1]. Interestingly, a statistically significant difference was observed in the Mon3 subset when the number of cells was determined (cells/μL). Moreover, Mon3 monocytes showed a significant protective association with all-cause death [1]. Moreover, the number of Mon 3 monocytes was found to be unchanged or reduced in the first week after STEMI [14] and increased in CHF [9][1] even after acute exercise [5]. In a specific comparison related to the levels of this monocyte subset, valvular patients (patients with CHF and valve defects) showed lower percentages (6.7 ± 3.4 versus 8.2 ± 4, $p = 0.04$) and numbers of cells (35.2 (23.7–63) versus 49.1 (34.7–70), $p = 0.01$) than ischemic patients and patients with dilated cardiomyopathy (8.3 ± 3.3, $p = 0.03$ and 49.7 (36.5–77.3), $p = 0.006$, respectively) [1]. Notably, there were no

differences observed in the level of the Mon2 subset between CHF etiologies. However, a statistically higher percentage of Mon3 monocytes was found in deceased patients [1].

It is worth noting that the amount of Mon1 monocytes in patients with ischemic HF was close to the values observed in patients with coronary artery disease without HF (the control group) [16]. However, the level of Mon1 increased during HF decompensation. Mon1 monocytes are also known to be involved in myocardial remodeling at sites of dying cardiomyocytes.

Notably, the presented studies on the distribution of monocyte subsets in CHF possess limitations related to the following factors: (i) small numbers of patients; (ii) unequal sizes between analyzed groups, and (iii) incomplete description of comorbidities that might be responsible for the abnormal release of monocytes. Moreover, it is complicated to compare the results because of different causes of CHF and different patient conditions between studies. Nevertheless, it is suggested that Mon2 monocytes predominate in the presence of surviving HF and that the cytokines and chemokines these monocytes release lead to the fibrosis of healthy heart tissue. Thus, as a result, the left ventricular relaxation in diastole is impaired. In contrast, Mon1 monocytes are found to be involved in myocardial remodeling at the site of dead cardiomyocytes. However, it is also possible that a different subset of monocytes involved in myocardial remodeling changes over time with different causes of heart failure and differences in pathogenesis. Thus, the monocyte distribution in patients with different CHF causes and conditions is still not yet well understood. There is, moreover, a lack of knowledge about differences in the monocyte subset distribution of HF caused by idiopathic cardiomyopathy, hypertension, obesity, ischemic heart disease and other factors. More complete knowledge about the differences in monocyte subtypes depending on the severity of CHF, and how these subtypes change following NYHA functional class changes, is also required. The role of sex in the formation of monocyte subsets in both healthy and CHF individuals also remains unclear.

2. Influence of Monocyte-Secreted Cytokines and Inflammatory Readings on HFrEF and HFpEF Development

Monocytes and macrophages were found to be essential to wound healing and tissue repair through angiogenesis, phagocytosis and favorable remodeling of the extracellular matrix [17]. However, prolonged inflammation leads to harmful remodeling [18] when the cells synthesize too much fibroblast and collagen content, promoting the apoptosis of cardiomyocytes [19].

Inflammation plays different roles in the onset and progression of HF in HFrEF and HFpEF [1][20][21][22]. Fibrosis occurs and is differentially managed between these two HF groups. Ischemic heart disease and cardiomyocyte loss lead to HFrEF [23]. It was previously documented that MI and, subsequently, heart muscle necrosis cause systemic and cardiac inflammation, which involves the activation of monocytes [24]. Activated monocytes produce cytokines and chemokines and thus further promote inflammation [24]. Late cardiac remodeling after MI includes the remodeling of both infarcted and non-infarcted myocardia since: (i) the unaffected myocardium strives to compensate for the function of the impaired heart area; (ii) the damaged myocardium is replaced by a collagen scar, and (iii) this scar expands into the healthy area [25]. In addition, the TNF-α secreted by monocytes triggers

uncontrolled oxidative stress, cardiomyocyte apoptosis, and even tissue necrosis [26][27]. The loss of cardiomyocytes contributes to the deterioration of heart muscle contractile functions and thus to the development of HFrEF [28]. Moreover, the excessive and prolonged infiltration of monocytes/macrophages into the damaged myocardium causes harmful inflammatory responses that can lead to cardiac fibrosis and adverse myocardium remodeling when LVEF becomes reduced and is insufficient to provide tissues with the necessary supplements and oxygen [29].

Chronic hypertension, cardiomyopathy, and valvular heart disease alter the metabolism in cardiac tissue and can cause HFpEF [30]. It was proposed that HFpEF can be regarded as low-grade chronic systemic inflammation featuring an activated nuclear factor kappa B (NFkB) pathway and the synthesis of pro-inflammatory cytokines and chemokines [30]. The released molecules subsequently activate hematopoietic cells in the bone marrow and spleen, which leads to low systemic inflammation and an increased number of blood leukocytes, neutrophils and monocytes [31]. Furthermore, Mon1 monocytes enter the heart tissue and become the pro-fibrotic macrophage subset (M2) [32], which activates fibroblasts. The activated fibroblasts then synthesize more collagen and fibronectin, which leads to increased myocardial stiffness [23][31]. In this case, the LVEF is normal, but the diastolic function becomes impaired through the prolonged LV relaxation and filling, increased diastolic stiffness, and elevated LV end-diastolic pressure [33]. It is thought that LV stiffness is caused by reduced Ca^{2+} signaling and titin modifications [30]. Notably, cardiac stiffness leads to extracellular matrix changes, cardiac fibrosis, and hypertrophy of cardiomyocytes. These hypertrophic changes result in diastolic dysfunction [34].

The functional diversity of monocytes and macrophages and their ability to contribute to different cardiac processes depend on phenotypic plasticity [35]. However, it remains unclear how the balance of monocyte subsets in both HFrEF and HFpEF is achieved. It seems that certain cytokines and chemokines are factors that determine monocyte subsets and clinical outcomes. For instance, 1.3- to 2.4-fold increased systemic levels of inflammatory markers (TNF-α, IL-6) and chemokine CCL2 were observed in worsening HFpEF compared to stable disease, suggesting that intensified inflammation may contribute to clinical worsening in HFpEF patients [36][37]. Moreover, the twofold increased level of macrophages in myocardial biopsies from HFpEF patients and the 59% stimulated expression of pro-fibrotic cytokine transforming growth factor beta (TGF-β) (compared to control) were associated with fibroblast activation and the excess deposition of collagen [31][38]. Importantly, HFpEF patients also had two- to four-fold elevated circulating levels of neutrophils and Mon1, Mon2, and Mon3 monocytes, while the levels of circulating lymphocytes were not affected [31][35]. These results suggest the development of chronic inflammation during HFpEF.

Another study showed that the seven-day incubation of primary monocytes from healthy subjects in cell media containing 10% serum from HFpEF patients stimulated the differentiation of monocytes into IL-10-expressing M2 macrophages [35]. Thus, long-lasting stimulation in HFpEF patients could push emerging macrophages towards a fibrogenic phenotype, thereby promoting myocardial collagen deposition and diastolic dysfunction. Notably, the synthesis of IL-10 was found to be beneficial in heart tissue repair and the resolution of inflammation following acute injury, thus preventing HFpEF after MI [39][40]. In contrast, IL-10 was found to evoke adverse effects in chronic conditions by promoting myocardial fibrosis and diastolic dysfunction in HFpEF [31]. The fact that the same

pathways could result in a positive outcome in HFrEF but could lead to pathology in HFpEF should be kept in mind when designing novel therapeutic strategies to limit disease progression in HF with diverse etiologies.

It was also shown that among HFrEF patients separated into two groups according to neutrophil count (relatively low and high), the CRP and fibrinogen concentrations and monocyte count were higher in the group with a higher neutrophil count [9][11]. These observations are in line with the low inflammatory environment observed in HFrEF patients. Regardless of the cause of HFrEF, inflammation results in cardiac remodeling evoked by cardiomyocyte damage and loss due to cardiomyocyte autophagy, apoptosis and necrosis [9]. In addition, metabolic risk factors in HFpEF occur under chronic low systemic inflammation together with the stimulated expression of adhesion molecules on the endothelial cells, which lead to systemic and local inflammation. Furthermore, the circulating levels of pro-inflammatory markers (IL-6, TNF-α) and acute inflammatory CRP were found to be higher in HFpEF than in HFrEF [36][41]. It was recently found that in HFrEF patients, the monocyte percentage and count were statistically significantly the highest in the NYHA IV group, while the NYHA functional class correlated with the total monocyte count and percentage (r = 0.172) [10]. In addition, the CRP concentration correlated with NT-proBNP (r = 0.203) [10]. Therefore, it can be assumed that the more affected the heart muscle, the stronger the pro-inflammatory environment in patients with chronic HFrEF.

Compounds released into the environment from dying cardiac cells stimulate M2 macrophages (arising from Mon1) to produce anti-inflammatory cytokines, including IL-10 and TGF-β, which preserve neighboring tissue and cardiac functions. Dying cardiomyocytes also secrete damage-associated molecular patterns (DAMPs), including double-stranded DNA. The recognition of DAMPs by M1 macrophages promotes the secretion of pro-inflammatory cytokines, including IL-1β, and leads to collateral tissue damage, adverse ventricular remodeling, and systolic dysfunction [42]. Over months to years, systemic neuroendocrine activation and compensatory mechanisms such as LV wall thinning and chamber dilation lead to HFrEF and its progression [43].

It is also known that in HFrEF patients, the levels of IL-1β and TNF-α can increase two- to six-fold compared to the levels in control subjects, thus signaling worse outcomes [44][45]. Therefore, it is proposed that macrophage-mediated inflammation plays a crucial role in HFrEF pathogenesis. Moreover, failure to clear apoptotic cardiomyocytes can lead to secondary necrosis and the release of DAMPs, which further stimulate pro-inflammatory reactions and collateral tissue injury. Therefore, the increased population of cardiac M1 macrophages in the ischemic heart and persistent inflammation transform the hematopoietic compartment and lead to further macrophage infiltration into the heart, causing harmful remodeling, systolic dysfunction and HFrEF progression (**Table 2**).

Table 2. The differences between HFpEF and HFrEF in monocyte and macrophage subsets, pathogenesis and myocardial changes [30][36][37][38][39][41][42][43].

HFpEF	HFrEF	
Predominant monocyte subset in	$CD14^{++}$, $CD16^{+}$ (Mon2)	$CD14^{++}$, $CD16^{-}$ (Mon1)

HFpEF	HFrEF	
the myocardium		
Differences in pathogenesis	Low-grade systemic inflammation; monocytes produce chemokines (MCP-1, TNF-α, TGF-β, IL-6).	Cardiac inflammation; fibrosis is associated with monocyte surface TLRs and the migration of Mon1 monocytes into the myocardium due to increased levels of IL-1β and CCR2 expression.
Macrophage subset	M2	M1
Myocardial changes	LV stiffness is caused by reduced Ca^{2+} signaling; conversion of titin into a less flexible form; perivascular and interstitial fibrosis; fibrotic changes in extracellular matrix and cardiomyocyte hypertrophy; impaired relaxation of the heart muscle	Collagen scar formation; cardiomyocyte apoptosis; impaired myocardial contraction

CD14: a glycosylphosphatidylinositol (GPI)-anchored receptor known to serve as a co-receptor for several Toll-like receptors (TLRs), both at the cell surface and in the endosomal compartment; LV: left ventricle; CD16: a type I transmembrane low-affinity receptor for IgG (FcγRIIIa); CD36: a class B scavenger receptor; CCR2: C-C chemokine receptor type 2 (CD 192); TNF-α: tumor necrosis factor α; IL: interleukin; MCP-1: monocyte chemoattractant protein 1 (a key chemokine that regulates monocyte migration); TGF-β: transforming growth factor beta (a multifunctional cytokine).

Furthermore, macrophage migration inhibitory factor (MIF; the inflammatory cytokine) mediates the pro-inflammatory effects that lead to fibrotic remodeling in HF due to non-ischemic cardiomyopathy with reduced LVEF. Furthermore, MIF expression is statistically significantly correlated with the degree of myocardial fibrosis (r = 0.51) [46]. The main differences between HFpEF and HFrEF in monocyte and macrophage subsets, pathogenesis, and myocardial changes are presented in **Table 2**.

Overall, there is still an ongoing debate as to whether the functions of monocytes and macrophages should be regarded as causes or consequences in human CHF development. Despite the findings that Mon2 is more important in HFpEF and Mon1 in HFrEF, further investigations are needed to define the interchange of signals between macrophages and other cardiac resident cells such as monocytes, fibroblasts, and cardiomyocytes. Moreover, the influence of comorbidities (diabetes mellitus, anemia, respiratory diseases, arrhythmias, and others) and risk factors (such as obesity, hypertension, and myocarditis) on the levels of monocyte and macrophage subsets and their functions must also be determined to revise existing therapeutic strategies. Thus, the choice of inflammatory cytokines as a therapeutic target and the monocytes themselves necessitate more research on this topic, as existing studies are not sufficient to prove certain targets for the treatment under consideration.

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