Special Article

Coronary Circulation in the Failing Heart

Yukio Maruyama, MD, Tomiyoshi Saito, MD, and Kazuhira Maehara, MD

SUMMARY

In congestive heart failure, vascular resistance increases because of vasoconstriction caused by activation of the neurohumoral system. On the other hand, vasodilatory responses can partially compensate for vasoconstriction by increasing vasodilatory substances. Although vasoconstrictive forces predominate as a whole, there is heterogeneity in the responses of different vascular beds to vasoactive agents. Especially, as for coronary circulation in the setting of heart failure, many factors may cause disturbances in coronary circulation. Thus, in this review, we discuss from the point of view of neurohumoral modification of coronary flow, coronary flow reserve, endothelial dependent and independent control of vasomotor tone, vascular responses in relation to vessel size or the severity of heart disease, and mechanical factors that determine coronary circulation. Throughout these discussions, the mechanism responsible for the reduction in coronary dilatory capacity is also described. Depressed myocardial blood flow and a blunted flow response to cardiovascular stimulation together may be one important mechanism responsible for the progression of disease in patients with cardiac dysfunction. Accordingly, even though it is not known whether abnormal coronary circulation is a cause or effect of heart failure, the treatment of impaired coronary flow reserve seems to be essential in the care of patients with cardiac dysfunction. (Jpn Heart J 1997; 38: 755–767)

Key words: Coronary circulation, Heart failure, Neurohumoral factors, Coronary pressure-flow relationships, Coronary flow reserve, Endothelium-dependent vasodilation

IN congestive heart failure, systemic vascular resistance increases because of vasoconstriction caused by an increase in the concentration of circulating norepinephrine and/or sympathetic nerve activation. The release of vasoconstrictive substances such as angiotensin II, vasopressin, and endothelin resulting from activation of the neurohumoral system also contributes to the increase in vascular resistance. Moreover, mechanical factors such as vessel stiffness due to sodium retention in the vascular wall limit vasodilation. On the other hand, vasodilatory responses can compensate for vasoconstriction by increasing plasma...
concentrations of vasodilatory substances such as prostaglandins and atrial and brain natriuretic peptides (ANP, BNP). Although vasoconstrictive forces predominate, there is heterogeneity in the responses of different vascular beds to vasoconstricting or vasodilating agents. It has been reported that vascular resistance increases with heart failure in the renal, splanchnic, and cutaneous perfusion beds, which have a high density of α receptors. As a result, in severe heart failure, renal and splanchnic flow may be reduced to 40% and 70% of normal, respectively. 1)

Chronic heart failure is a clinical syndrome characterized by a decrease in cardiac output, which is due, in part, to an increase in vascular resistance. In addition to neurohumoral modification of resistant vessels in the setting of heart failure, disturbances in coronary circulation may be caused by compensatory mechanisms or by congestive heart failure itself. Specific mechanisms that are involved: (a) the Frank-Starling mechanism in which an increase in the ventricular end-diastolic pressure or volume inhibits coronary inflow; (b) left ventricular hypertrophy, in which the increased mass of the heart causes inhibition of coronary inflow; (c) dysfunction of endothelial dependent and independent coronary vasodilation; and (d) disturbance in coronary circulation as a result of changes in subendocardial myocardial perfusion or metabolism. 2) Despite these disturbances in coronary circulation, resting coronary blood flow is generally preserved until the later stages of heart failure. 1,3-7)

The changes that occur in the coronary circulation with congestive heart failure depend on a number of variables. In this review, we discuss modulation of coronary circulation in heart failure, especially from the point of view of neurohumoral modification of coronary flow, coronary flow reserve, endothelial dependent and independent control of vasomotor tone, vascular responses in relation to vessel size or the severity of heart disease, and mechanical factors that determine coronary circulation.

Neurohumoral Modification of Coronary Circulation

Previous studies have demonstrated that vasoconstriction is enhanced in heart failure, although compensatory induction of vasodilatory systems also occurs. 8,9) Plasma norepinephrine, which is known to stimulate sympathetic α1-receptors and induce vasoconstriction, increases with worsening heart failure. 9) As a result, plasma norepinephrine concentration is an independent predictor of prognosis in patients with congestive heart failure. 10) Further, systemic vascular resistance in congestive heart failure increases two-fold in response to increased circulating levels of norepinephrine. 11-14) According to Creager et al., 15) systemic vascular resistance decreased by the greatest amount with inhibition of α1-recep-
tors by phentolamine, when compared to vasodilation induced by arginine vaso-
pressin antagonists or angiotensin converting enzyme inhibitors. Further, postsynaptic $\alpha_2$-adrenceptors mediate vasoconstriction in the coronary, brachial, and femoral vascular beds.\textsuperscript{16,17} However, preservation of coronary blood flow has been reported both in patients and in experimental models of congestive heart failure.\textsuperscript{1,4,5}

With respect to adrenergic responses within the coronary vasculature, vascular smooth muscle contraction is mediated by $\alpha_1$- and $\alpha_2$-adrenceptors.\textsuperscript{18,19} However, $\alpha_2$-adrenceptor-mediated vasodilation occurs through the release of endothelium-derived relaxing factor (EDRF).\textsuperscript{20,21} Recent studies have demonstrated augmentation of endothelium-dependent relaxation in response to norepinephrine in the setting of heart failure, suggesting that $\alpha_2$-adrenceptor-mediated vasodilation may serve as an important protective mechanism to maintain coronary blood flow.\textsuperscript{3,22} Moreover, in contrast to the $\beta$-adrenceptor, the postsynaptic $\alpha_2$-adrenceptor remains active in maintaining vasoconstriction despite increases in plasma norepinephrine concentrations in heart failure.\textsuperscript{16} It must be kept in mind that postsynaptic $\alpha_2$-adrenceptors are preferentially activated by circulating, rather than neuronally-released, norepinephrine.\textsuperscript{23,24} However, O'Murchu et al. pointed out that endothelial responses have only been studied in large epicardial conduit arteries, not resistance vessels.\textsuperscript{3} Therefore, we must be careful in extrapolating these results to coronary blood flow regulation in the coronary microcirculation. Moreover, coronary atherosclerosis or coronary hypoperfusion may influence the vasoconstrictive response of the coronary arteries modulated by $\alpha_2$-adrenceptors,\textsuperscript{25,26} although the effects of atherosclerosis and hypoperfusion remain controversial.\textsuperscript{27} Therefore, it remains unclear how the regulation of $\alpha_2$-adrenceptor-mediated vascular tone is affected by the cause of heart failure.

There are substantial data which indicate that the renin-angiotensin system and the sympathetic nervous system contribute individually to increased systemic vascular resistance. In addition, these systems interact with each other, with increased plasma concentrations of catecholamines and angiotensin II,\textsuperscript{28,29} causing a deterioration of pump function.\textsuperscript{10,30} Angiotensin II is a potent vasoconstrictor of vascular smooth muscle, and both circulating levels of angiotensin II and tissue angiotensin II levels increase in the setting of heart failure. It has been shown that intracoronary administration of the angiotensin converting enzyme inhibitor, enalaprilat, induces coronary vasodilation, reducing coronary resistance by approximately 20\% without stimulating the peripheral renin-angiotensin system.\textsuperscript{31} It is of interest that another angiotensin converting enzyme inhibitor, captopril, administered orally, decreases systemic vascular resistance by 20\% in patients with congestive heart failure.\textsuperscript{15} This reduction in coronary or systemic
vascular resistance is less than that induced by $\alpha$-adrenoceptor antagonists. However, it should be noted that angiotensin II is produced not only by the angiotensin converting enzyme, but also by the serine proteinase, chymase.\(^{32,33}\) Therefore, angiotensin converting enzyme inhibitors cannot completely inhibit angiotensin II. According to Okunishi et al. only 30% to 40% of the conversion of angiotensin I to angiotensin II is catalyzed by the angiotensin converting enzyme, while the rest of the angiotensin II is formed by the action of a chymase.\(^{32}\) However, it is unclear how important this angiotensin converting enzyme independent pathway is for controlling in vivo coronary vascular tone and systemic vascular resistance in humans, because of the unavailability of a specific chymase inhibitor. Another reason why the actions of angiotensin converting enzyme inhibitors are not totally dependent on the inhibition of angiotensin II alone is because of the inhibition of endogenous kinin degradation.\(^{34}\) As a result, bradykinin increases and causes dilation of coronary vessels in the normal circulation through the release of NO, prostacyclin, and hyperpolarizing factor\(^{35,36}\) from the endothelium.\(^{35,36}\) However, it remains unclear what role increased bradykinin plays in regulating the coronary circulation in heart failure.

Increases in other vasoconstrictor substances such as vasopressin\(^{15}\) and endothelin\(^{37,38}\) also have been reported in heart failure, although only one third of patients with congestive heart failure have increased concentrations of vasopressin.\(^{15}\) Thus, the contribution of vasopressin to the increase in systemic vascular resistance appears to be minor. However, the role of vasopressin in controlling coronary vascular tone in heart failure is not well understood. With respect to plasma endothelin concentrations, two- to three-fold increases in circulating endothelin have been demonstrated in congestive heart failure.\(^{39}\) Endothelin is an endothelium-derived peptide that increases in concentration in the setting of congestive heart failure in response to elevated atrial and venous pressures, reduced perfusion pressure, and shear stress.\(^{37}\) In the heart, endothelin mRNA expression increases in pathophysiologic states. It is therefore likely that the coronary circulation may be affected by endothelin production.\(^{37,40}\) It is of interest that endothelin causes potent coronary vasoconstriction with associated activation of the renin-angiotensin system.\(^{41}\) Moreover, elevation of circulating concentrations of tumor necrosis factor occurs with marked activation of the renin-angiotensin system and has been reported in severe chronic heart failure.\(^{42}\)

In contrast to the elevation of plasma concentrations of vasoconstrictor substances in the setting of heart failure, various neurohumoral factors which reduce vascular resistance are produced to protect against excessive vasoconstriction. Atrial and brain natriuretic peptides,\(^{43-45}\) adrenomedullin,\(^{46}\) and prostaglandins\(^{8}\) cause vasodilation. With respect to prostaglandins, the production of vasoconstrictive prostaglandins tends to exceed the production of vasodilatory pros-
taglandins in the forearm in patients with heart failure. 47) Little is known about the effects of the other vasodilatory agents in coronary flow maintenance.

**ENDOTHELIUM-DEPENDENT REGULATION OF CORONARY CIRCULATION**

In the setting of volume or pressure overload, increased metabolic demand is accompanied by elevated coronary blood flow, which is induced by the production of a "metabolic dilator" such as adenosine. 48) Endothelium derived relaxation factor (EDRF) acts to augment the increase in coronary flow through increases in adenosine. 49) This adaptation to increased cardiac work through EDRF seems to be essential for the maintenance of cardiac mechanical function in the normal or compensated state of the heart. In heart failure, however, the ability of large and small coronary arteries to produce EDRF (nitric oxide) with acetylcholine stimulation, is clearly reduced. 50-52) Moreover, the effects of acetylcholine and substance P, an endothelium-dependent vasodilator, on the coronary resistance vessels were depressed in patients with dilated cardiomyopathy compared to control patients, although the responses of the epicardial coronary arteries were similar in both groups. 53-56) This dysfunction of endothelium-dependent vasodilation in the coronary microvasculature also was demonstrated in an asymptomatic patient with an early cardiomyopathy.57)

In contrast, the nitric oxide dependent dilation of large coronary arteries is significantly increased in the early stages of decompensated heart failure. 49) These results indicate that NO production in the large coronary arteries following endothelial stimulation is largely influenced by the severity of the heart failure. However, there are no data concerning the response of small vessels to NO production in the early stages of heart failure. Even if the ability of the vascular endothelium to generate EDRF following endothelial stimulation decreases in advanced heart failure, an attenuated response of EDRF release does not necessarily indicate an overall reduction in endothelial function. In fact, the basal production and/or release of NO into the coronary circulation has been shown to be enhanced in the setting of heart failure by (1) increased shear stress, 49) (2) activation of ETb receptors, 58) (3) activation of the α2-receptor, 3, 59) and (4) increased production of cytokines. 4, 60) Moreover, Drexler et al. 50) demonstrated that if EDRF synthesis and release occur at nearly maximal rates, additional stimuli may lead to only limited further vasodilatory responses. In fact, although endothelium-dependent responses to acetylcholine are impaired in congestive heart failure because of a reduced release of NO, the basal release of NO appears to be enhanced. This was demonstrated by blockade of the basal release of NO by an inhibitor of nitric oxide production, L-NMMA, which resulted in an exaggerated vasoconstrictor response in patients with heart failure. 50) This finding was observed in
several vascular beds (hindquarter, renal, and intestinal vessels) in a rat heart failure model, as well as in the forearm and systemic vascular beds of patients with chronic heart failure. In contrast, the basal level of nitrite released from large coronary arteries and microvessels isolated from failing hearts is significantly less than in vessels from normal hearts. Thus, the amount of basal NO production in the coronary circulation remains controversial. Additionally, in vivo NO production in the coronary vascular beds has not been studied in the basal state in the failing heart.

Recently, we studied systemic vascular resistance and diastolic coronary vascular resistance in the pacing-induced canine heart failure model. The diastolic coronary pressure-flow relationship is minimally influenced by cardiac contraction or metabolic regulation. Further, the slope of this relationship corresponds to coronary resistance. Thus, the diastolic coronary pressure-flow relationship should provide better information about coronary circulation than the calculated resistance. In our study, the basal coronary flow increased 3 weeks of pacing at 240/min, and the slope of the diastolic coronary pressure-flow relationship became steeper without a significant change in the measured zero-flow pressure. After administration of a NO synthesis inhibitor, the slope of the coronary pressure-flow relationship in the heart failure group decreased more than before heart failure. These results indicate that basal coronary flow is maintained by basal NO production in small coronary arteries. Further, NO-mediated increases in coronary flow are not necessarily impaired in chronic heart failure, at least not in the early stages of decompensated heart failure. However, it is unclear from this study whether basal NO production decreases after the development of severe congestive heart failure as previously suggested. Furthermore, decreased, unchanged, and increased basal coronary flow have all been reported and there is still controversy concerning basal coronary flow in heart failure, as noted in the production of basal NO.

**Coronary Flow Reserve in Heart Failure**

The vasodilatory capacity of the coronary resistance vessels has been evaluated during atrial pacing, after dipyridamole, adenosine, or papaverine infusions. Previous reports indicate that the endothelium-independent vasodilatory capacity decreases or tends to decrease in patients with idiopathic dilated cardiomyopathy. The reduction in vasodilatory capacity also has been demonstrated in various types of nonischemic cardiomyopathy and hypertrophic heart diseases.

The mechanism responsible for the reduction in coronary dilatory capacity is complex, and increased extravascular myocardial compressive forces have been
implicated. Specifically, increases in cardiac dimension and filling pressure cause an increase in wall tension. In addition, increased heart rate and increased ventricular mass discussed later are conceivable for a reduction in coronary flow reserve, as well as decreased coronary perfusion pressure. However, it has been reported that neither an elevated left ventricular diastolic pressure nor a low coronary perfusion pressure can clearly explain the reduction in coronary flow reserve. Most studies have found no microvascular structural abnormalities in tissue specimens from patients with dilated cardiomyopathy. In contrast, morphologic changes in microvascular vessels have been noted in hypertrophic hearts. However, intrinsic microvascular dysfunction may be present because abnormal myocardial blood flow responses to pacing tachycardia and to dipyridamole infusion occur independent of hemodynamic factors in patients without evidence of overt heart failure. This study strongly suggests that depressed myocardial blood flow and a blunted flow response to cardiovascular stimulation may be one mechanism responsible for the progression of disease in patients with advanced dilated cardiomyopathy. The question of whether coronary vasodilator reserve is impaired in heart failure irrespective of the cause of failure is not fully resolved. However, at least in hypertensive heart failure and/or hypertrophic cardiomyopathy, a reduced coronary flow reserve is likely to initiate a process of hypoperfusion, leading to the development of heart failure.

**MECHANICAL MODIFICATIONS OF CORONARY CIRCULATION IN HEART FAILURE**

In heart failure, the ventricular filling pressure, ventricular diastolic volume, and heart rate increase while ventricular developed pressure, cardiac contractility, and aortic pressure decrease or tend to decrease. Therefore, the driving pressure for coronary perfusion [diastolic aortic pressure minus right atrial pressure (i.e., downstream pressure)] seems to fall. In fact, an increase in the filling pressure impedes coronary inflow and an elevated downstream pressure causes an increase in the zero-flow pressure of the coronary pressure-flow relationship without changing the slope of the relationship. In addition, the inhibitory effects of increased diastolic filling pressure on coronary inflow are augmented if the pericardium is acutely stretched. Thus, increased ventricular filling pressure implies impairment of coronary inflow. Furthermore, right atrial pressure or coronary venous pressure, which acts as back pressure for the coronary circulation, also determines the zero-flow pressure of the coronary pressure-flow relationship. Satoh et al. and Farhi et al. directly observed “waterfall” behavior via the effects of increased outflow pressure by right atrial and ventricular pressure elevation. In other words, there is a threshold or level of downstream pressure that affects coronary inflow, and coronary inflow is not influenced by
pressure below this threshold level. However, Scheel et al. studied the direct influence of coronary sinus pressure on zero-flow pressure. Based on their findings, it is highly probable that an increase in right atrial pressure disturbs coronary inflow in the failing heart.

It is of further interest how increases in back pressure during systole or diastole impair coronary inflow dynamics. Synchronized retroperfusion, which is used clinically to support ischemic myocardium by delivering arterial blood in a retrograde fashion through the coronary sinus during diastole, decreases coronary driving pressure in diastole and may disturb coronary circulation. On the other hand, coronary venous drainage occurs during systole; therefore elevated back pressure during systole increases the intravascular blood volume contained in the heart by inhibiting venous drainage. This may induce impairment of coronary inflow. Systolic back pressure elevation probably occurs in pathologic conditions such as constrictive pericarditis, pericardial tamponade, and acute cardiac distension. Whether increased back pressure in diastole or systole has a greater effect on coronary inflow has yet to be determined. To examine this problem, the coronary pressure-flow relationship has been compared in the setting of the two types of back pressure elevation. Based on this study, synchronized retroperfusion with increased diastolic downstream pressure does not significantly impair coronary arterial inflow, compared with increased systolic coronary sinus pressure. The reason why synchronized retroperfusion slightly impedes coronary inflow is that synchronized retroperfusion preserves the squeezing effect of systole which promotes coronary inflow. Diastolic back pressure elevation can also augment collateral flow in contrast to the reduction in flow to the collateral-dependent myocardium which can occur with increased back pressure that is not limited to diastole.

Coronary arteries are embedded in the myocardium, so that heart rate and extravascular systolic and diastolic compressive forces, which are determined by several variables including ventricular pressure and cardiac dimension, affect coronary arterial tone and phasic flow. In heart failure in which tachycardia and an enlarged ventricular chamber are common, coronary vascular resistance may be modified by these mechanical effects. In addition, the effects of afterload impedance on coronary circulation, as well as the coronary perfusion pressure itself, must be taken into account in the setting of decreased arterial compliance. Conversely, pressure changes not only in the arterial tree, but also in the venous system, may alter ventricular compliance. Accordingly, interactions between the coronary vascular bed, extravascular mechanical factors, and the coronary and systemic circulations are believed to occur in congestive heart failure. Moreover, mechanical modulation of coronary circulation may be further influenced by various in vivo phenomena including activation of
the neurohumoral system.\textsuperscript{(102)}

Finally, the progression from the compensated state of cardiac dysfunction to overt heart failure is due to many factors. Among them, impaired coronary flow reserve is probably a primary factor. Even though it is not known whether abnormal coronary circulation is a cause or effect of heart failure, the treatment of impaired coronary flow reserve is essential in the care of patients with cardiac dysfunction. However, there has been little progress in the pharmacologic treatment of abnormal coronary circulation in heart failure. These issues, as well as the many unanswered problems mentioned above, should be the subjects of intensive investigation in the near future.

\textbf{ACKNOWLEDGMENT}

The authors thank Ms. Noriko Sato for her expert secretarial work.

\textbf{REFERENCES}


43. Tsutamoto T, Kanamori T, Morihani N, Sugimoto Y, Yamaoka O, Kinoshita M. Possibility of downregulation of atrial natriuretic peptide receptor coupled to guanylate cyclase in peripheral vascular beds of patients with chronic severe heart failure. Circulation 1993; 87: 70-5.


100. Schipke JD, Stocks I, Sunderdie KU, Arnold G. Effect of changes in aortic pressure and in coronary arterial pressure on left ventricular geometry and function: anrep vs garden hose effect. Basic Res Cardiol 1993; 88: 621–37.
