Neurohormonal Regulation and the Overlapping Pathology Between Heart Failure and Acute Coronary Syndromes

Robert L. Jesse, MD, PhD

Virginia Commonwealth University Health System, Veterans Health Administration, Richmond, VA

An understanding of the dynamic relationship between the coronary artery and left ventricular (LV) function is important in diagnosing and treating acute coronary disease. Measurement of B-type natriuretic peptide (BNP) provides rapid and accurate identification of patients with impaired LV function, which has proven valuable in differentiating between congestive heart failure (CHF) and symptoms attributable to pulmonary etiologies. Coronary artery and ventricular pathophysiology both are characterized by injury, functional aberrations, and subsequent remodeling. Ischemia occurs in both and accounts for virtually all significant adverse outcomes. The difference in BNP elevations seen in acute ischemia compared with those observed in chronic CHF is striking: Although even small BNP elevations in acute coronary syndromes have powerful prognostic value, it is not likely that they can be effectively used as a diagnostic marker for ischemia.
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Key words: Acute coronary syndromes • B-type natriuretic peptide • Congestive heart failure • Ischemia • Left ventricular function • Myocardial infarction

The single major cause of heart failure in the United States is myocardial ischemia and infarction. This disorder can manifest as both systolic and diastolic dysfunction and emphasizes the important interaction between coronary artery disease (CAD) and left ventricular (LV) function. This relationship is also evidenced by the important prognostic value of the left ventricular ejection fraction (LVEF) in predicting outcomes, both short and long term, in acute

Table 1
Killip Classification of Myocardial Infarction*

Class	Clinical Findings	Mortality	
		Killip	GUSTO
I	No signs of LV failure	6 %	5%
II	S3 gallop or basilar rales	13 %	14 %
III	Pulmonary edema	38 %	32 %
IV	Cardiogenic shock	81 %	58 %

*The Killip classification is a simple clinical assessment of left ventricular (LV) function that risk-stratifies patients based on the severity of chronic heart failure symptoms. The symptom-derived mortality reported in the original publication[5] is similar to that reported from the GUSTO study nearly 25 years later.[6]

ischemic coronary disease. Therefore, it is important to appreciate the dynamic relationship between the coronary artery and ventricular function in order to plan both diagnostic and treatment strategies.

Coronary Artery Occlusion and Ventricular Function

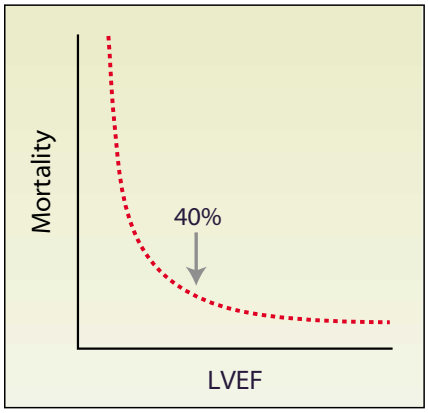
Early animal studies by Reimer and colleagues[1] set the stage for the "thrombolytic era" by demonstrating that the duration of myocardial ischemia resulting from coronary occlusion ultimately determined the extent of myocardial damage. The clinical application of that principle became the foundation for the "open artery hypothesis," which spawned the mantra "time is muscle." This very simple notion has been upheld through virtually every fibrinolytic trial, and similar efficacy has also been demonstrated for primary angioplasty. Although argument ensued regarding which is the superior strategy, it is now clear that urgent revascularization, by any means, has time-critical benefits in reducing mortality.[2] Quite simply, the mechanism through which coronary flow is restored is less critical than the timing of reperfusion relative to the onset of the occlusion.[3]

Even brief episodes of ischemia that don't result in necrosis can impact LV function. These can be seen as transient, rapidly reversible wall motion abnormalities following brief coronary occlusion or, in more severe cases, as myocardial stunning after prolonged ischemic insult.[4] It is clear, however, that, although perfusion status of the coronary artery—ie, Thrombolysis in Myocardial Infarction (TIMI) flow grade—affects outcome, it is the residual functional capacity of the left ventricle that is most directly linked to mortality. In fact, the single best predictor of mortality following an ischemic event is LV function. This can be seen at presentation through both the simple bedside assessment provided by the Killip classification (Table 1),[5] which was confirmed in the Global Utilization of Strategies to Open Occluded Coronary Arteries (GUSTO) trial,[6] and the relationship between post-myocardial infarction (MI) LVEF and survival (Figure 1).

Quite simply, the mechanism through which coronary flow is restored is less critical than the timing of reperfusion relative to the onset of the occlusion.

Given the relationship of LV function to outcomes, it is now standard procedure to quantify LVEF in the post-acute coronary syndrome (ACS) patient via echocardiography, angiography, or nuclear imaging. However, in acute settings such as the emergency department, these procedures are not necessarily available. Measurement of plasma hormones can also provide important information about LV function. The difficulty of assessing these markers has historically precluded their implementation into clinical protocols until the recent demonstration that a simple point-of-care assay for B-type natriuretic peptide (BNP) can rapidly and accurately identify patients with impaired LV function. This assay has proven to be of value in the emergency department diagnosis and triage of patients presenting with dyspnea because of its ability to differentiate congestive heart failure (CHF) from symptoms attributable

Figure 1. *There has been a well-characterized relationship between the left ventricular ejection fraction (LVEF) following myocardial infarction (MI) and mortality, which is nearly an inverse logarithmic relationship. This relationship holds for almost any time point, and events increase dramatically among patients with LVEFs <40%.*



to pulmonary etiologies. In addition, BNP carries valuable prognostic significance for predicting readmission and early mortality in CHF patients undergoing hospital-based treatment. The early implementation of BNP into clinical practice has thus focused on distinguishing those patients with suspected ventricular dysfunction.

As in CHF, ventricular loading parameters change during acute ischemic episodes. This suggests that BNP might be acutely elevated in ACS for reasons similar to those that occur in chronic CHF. This suggestion has led to a series of studies describing the diagnostic and prognostic value of BNP in ACS patients.[7,8]

Events that occur at the level of the coronary artery are mirrored by those of the ventricle. Figure 2 diagrams this relationship in some detail and, although at first glance it appears rather complex, it is not quite as daunting as it seems. The fundamental recognition must be that both coronary artery and ventricular pathophysiology are characterized first by injury of some form, then specific functional aberrations, and then subsequent remodeling processes. Events occurring to one will invariably affect the other, but ultimately, ischemia links the two and accounts for virtually all significant adverse outcomes either directly (ie, systolic and diastolic dysfunction, reperfusion arrhythmias) or indirectly through subsequent necrosis and impaired LV function or attenuation of other neurohormonal pathways.

For example, coronary risk factors, both genetic and environmental, can lead to vascular injury, and it is the response to this injury that is the basis for atherogenesis.[9] This sets the substrate for episodic plaque rupture and thrombus formation, which, in most cases, has no overt clinical consequences, though it does lead to remodeling of the

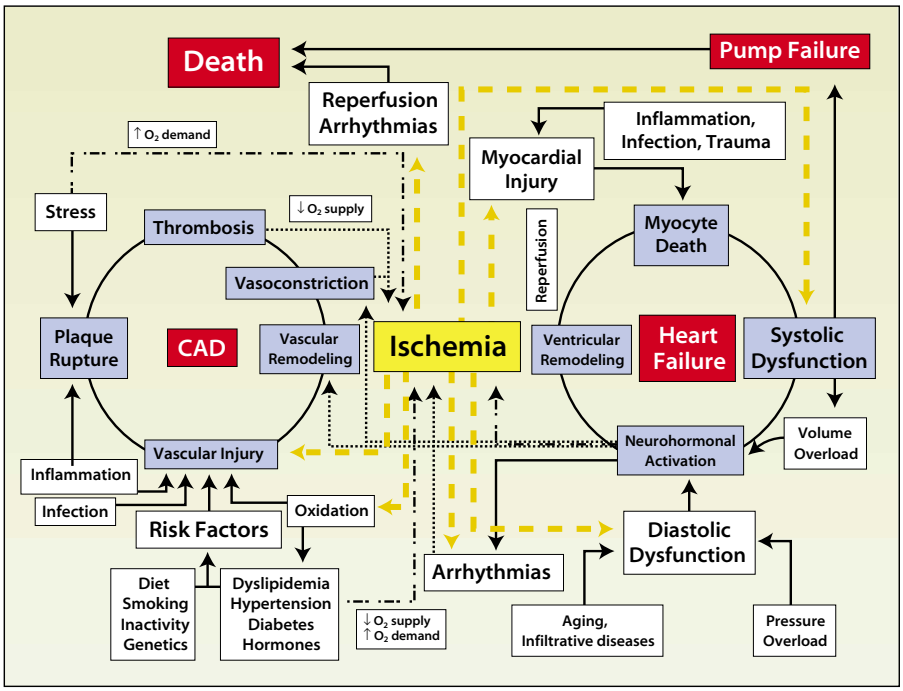


Figure 2. *The physiologic relationship between the coronary artery and the left ventricle. Both the coronary artery and ventricle are subject to injury and remodeling. Central to the interaction is the presence of ischemia generated by reduced blood flow or increased demands. CAD, coronary artery disease.*

artery.[10,11] Healing, ie, arterial remodeling, leads to fibrosis (and calcification), which likely serves to stabilize the plaque. However, if there is complete or high-grade, persistent occlusion, ischemia is likely to result. In the worst-case scenario, plaque rupture causes intracoronary thrombosis and high-grade coronary occlusion. Obstruction to blood flow results in ischemia, which leads to injury and, when prolonged, to myocyte necrosis. In this situation, there is initially ischemic diastolic dysfunction followed by systolic dysfunction, both of which are reversible. With the onset of necrosis, irreversible impairment in LV function occurs, the extent of which is directly related to the amount of damaged myocardium.

The above process can be mapped onto a diagram (Figure 3A), as can CHF (Figure 3B). Figure 3C demonstrates the feedback pathways for BNP and illustrates that BNP (neurohormonal activation) release in response to ischemia affects the system via amelioration of at least four mechanisms: 1) ischemia-induced systolic dysfunction, 2) ischemia-induced necrosis leading to systolic dysfunction, 3) ischemia-induced diastolic dysfunction, and 4) arrhythmias due to both ischemia and neurohormonal activation. The release of BNP serves to unload the ventricle directly but also directly affects the coronary arteries, causing dilation, thus relieving the underlying ischemia, which also unloads the ventricle.

The ability to measure BNP should thus provide important information about LV function. We know this to be true through the well-characterized relationship between BNP level and the extent of LV dysfunction.[12] It is then a logical assumption that an acute ischemic

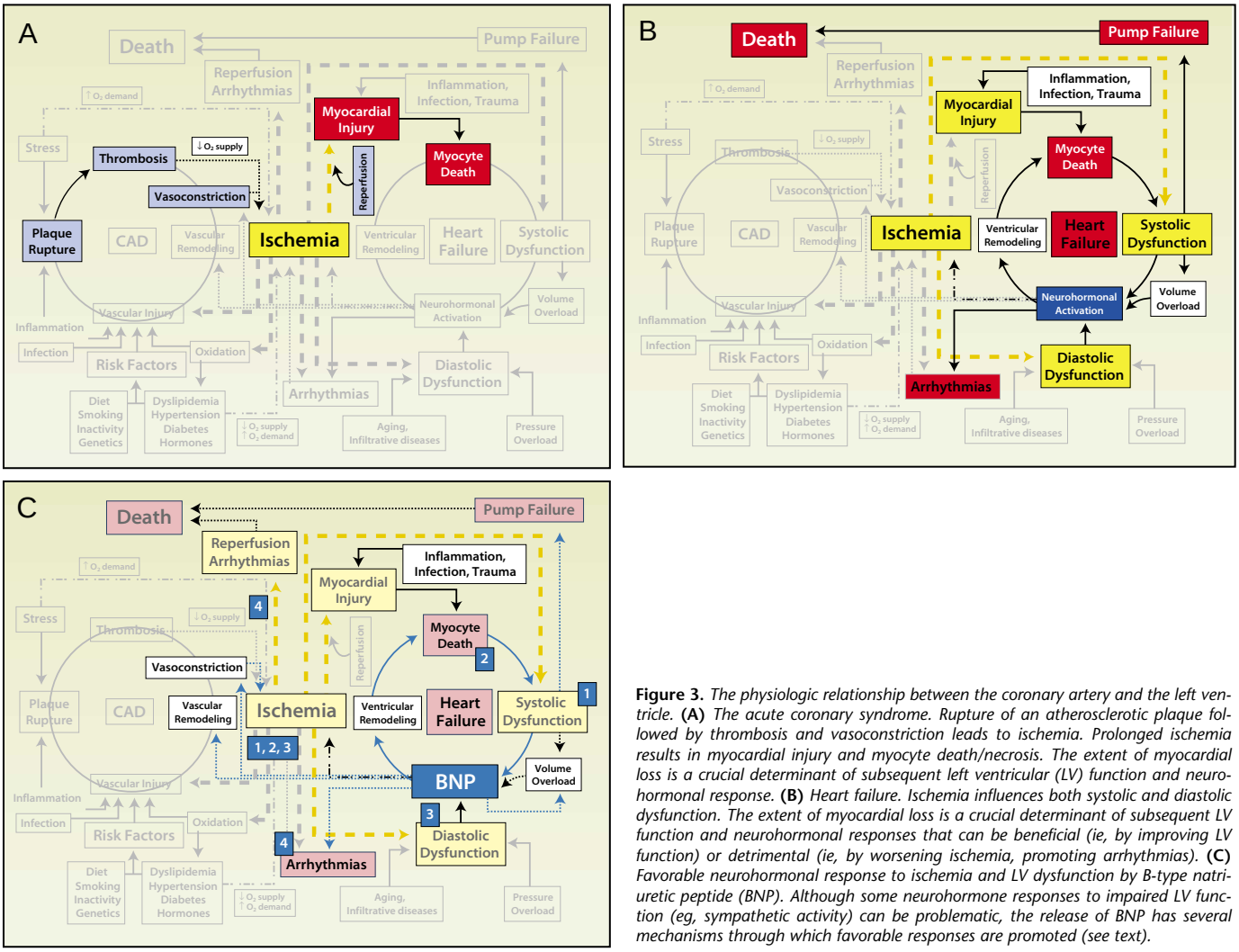


Figure 3. *The physiologic relationship between the coronary artery and the left ventricle.* **(A)** *The acute coronary syndrome. Rupture of an atherosclerotic plaque followed by thrombosis and vasoconstriction leads to ischemia. Prolonged ischemia results in myocardial injury and myocyte death/necrosis. The extent of myocardial loss is a crucial determinant of subsequent left ventricular (LV) function and neurohormonal response.* **(B)** *Heart failure. Ischemia influences both systolic and diastolic dysfunction. The extent of myocardial loss is a crucial determinant of subsequent LV function and neurohormonal responses that can be beneficial (ie, by improving LV function) or detrimental (ie, by worsening ischemia, promoting arrhythmias).* **(C)** *Favorable neurohormonal response to ischemia and LV dysfunction by B-type natriuretic peptide (BNP). Although some neurohormone responses to impaired LV function (eg, sympathetic activity) can be problematic, the release of BNP has several mechanisms through which favorable responses are promoted (see text).*

event, which we know increases LV filling pressures, should also result in the release of BNP. Proof of this principle was demonstrated prospectively by directly measuring BNP following balloon inflations during percutaneous transluminal coronary angioplasty[13] and has been confirmed in retrospective evaluation of samples from ACS trials. Omland and colleagues[14] showed that, for patients with unstable angina or non-ST-elevation acute MI who were enrolled in the TIMI-11B trial, N-terminal BNP prognosticated short-term (43-day) mortality. Similar findings were demonstrated by de Lemos and coworkers[7] in a retrospective analysis of BNP from patients with non-ST-elevation ACS enrolled in the TIMI-16 (Orbofiban in Patients with Unstable Coronary Syndromes [OPUS]) trial. Using a dichotomous cutoff of 80 pg/mL, the investigators found that BNP was a powerful predictor of mortality, both early (30-day) and longer term (10-month). This was confirmed by Morrow and associates[8] in an analysis of the TIMI-18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy [TACTICS]) trial. Also using a dichotomous cutoff of 80 pg/mL, the authors

Patients with elevated BNP at baseline had a nearly sixfold greater risk of developing heart failure (5.9% vs 1.0%, P < .0001) by 30 days. Importantly, this was independent of troponin status.

found that BNP was a powerful independent predictor of early (7-day) and short-term (30-day) mortality. Even more significant is that patients with elevated BNP at baseline had a nearly sixfold greater risk of developing heart failure (5.9% vs 1.0%, $P < .0001$) by 30 days. Importantly, this was independent of troponin status, which was confirmed by Sabatine and colleagues[15] in a multimarker approach to risk stratification of non-ST-elevation ACS showing additional value to BNP following troponin.

What do BNP elevations in ACS and CHF really tell us? Are they simply a reflection of the change in LV load and wall stress secondary to ischemia or remodeling following necrosis? The amount of BNP detected may provide important mechanistic information. There is a significant difference seen in levels of BNP measured following an acute insult compared with those seen in the setting of chronic CHF. As mentioned previously, it is common to detect BNP levels in the range of 400–500 pg/mL in mild to moderate CHF and well above 1000 pg/mL in moderate to severe heart failure. These levels are rarely seen in the setting of an acute ischemic event.

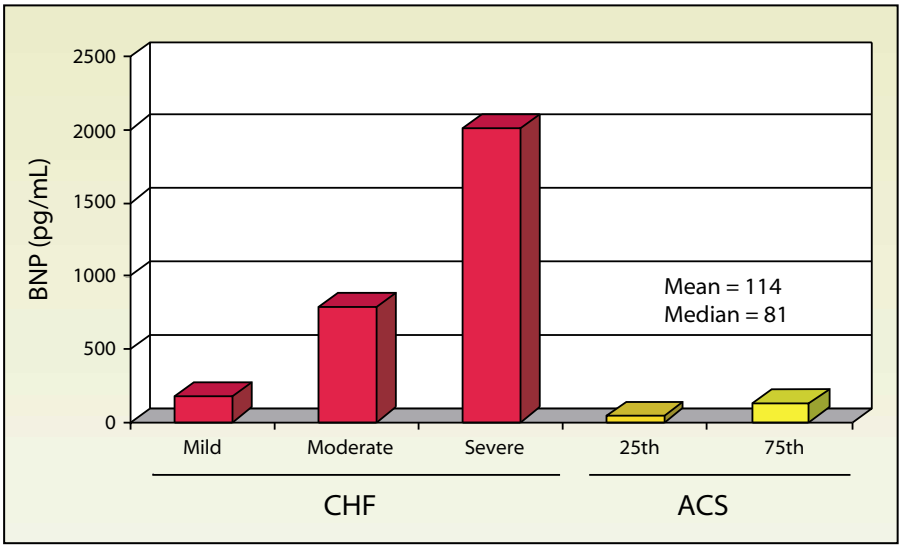


Figure 4. *Comparison of B-type natriuretic peptide (BNP) release in chronic heart failure (CHF) versus in acute coronary syndromes (ACS). The levels of BNP seen in CHF are significantly higher than those in ACS. Even mild CHF has levels well in excess of those for the 75th percentile of a high-risk non–ST-elevation (non-STE) ACS population.*

In the setting of non–ST-segment elevation ACS, there is predictive value to BNP elevations whether taken as a dichotomous cut point or observed in terms of levels by quartiles. de Lemos and coworkers[7] reported that BNP levels were higher among patients from a high-risk ACS population who had died at 30 days (153 pg/mL) compared with those who were alive (80 pg/mL). The adjusted odds ratio for mortality relative to quartile 1 was significantly increased in quartiles 2–4: 3.8 (range 1.1–13.3), 4.0 (1.2–13.7), and 5.8 (1.7–19.7), respectively. The interquartile BNP ranges are worth noting: Quartile 1 was 5.0–46.4 pg/mL, quartile 2 was 43.7–81.2 pg/mL, quartile 3 was 81.3–137.8 pg/mL, and quartile 4 was 137.8–1456.6 pg/mL. However, the mean for the entire population was 114 ± 126 pg/mL, with the median 81 pg/mL. The 25th and 75th percentile values were 44 pg/mL and 138 pg/mL, respectively, thus the majority of non–ST-elevation ACS patients had a BNP less than that seen in even mild CHF. In fact, the median BNP for this high-risk ACS-enriched population was almost exactly equal to the value chosen as the dichotomous cutoff by receiver-operating characteristic (ROC) analysis for a normal population.

The elevations of BNP seen with an acute insult are modest in comparison to those present in chronic CHF.

A similar situation is seen for BNP elevations in pulmonary embolism.[16] In a series of 73 consecutive patients presenting with pulmonary embolism, the 20 patients who had adverse clinical events had a higher median BNP (194.2, 3.7–1201 pg/mL) than those who had a benign clinical course (39.1, 1.0–1560 pg/mL). Importantly, there was no difference in the incidence of CAD or prior CHF between the two groups, and the patient with the highest BNP (1560 pg/mL) was a 75-year-old with New York Heart Association class III CHF who had a benign clinical course. It is important to note that the elevations of BNP seen with an acute insult are modest in comparison to those present in chronic CHF.

Low-level BNP changes were also observed in the setting of nonobstructive hypertrophic cardiomyopathy, in which there was, as might be expected, a slight increase in BNP secretion at baseline: 156.7 ± 104.1 compared with normal control patients (9.8 ± 9.6). Among the hypertrophic cardiomyopathy patients, BNP increased when ischemia was

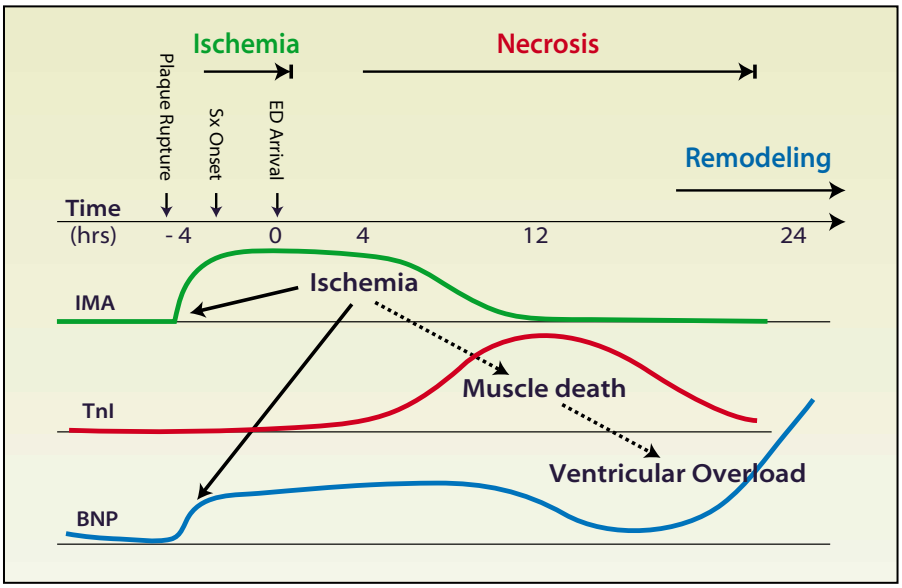


Figure 5. *The temporal relationship among ischemia, necrosis, and B-type natriuretic peptide (BNP). Following coronary occlusion, there is immediate ischemia, which can be detected by electrocardiography, albeit with low sensitivity, through myocardial perfusion imaging, as well as by presence in the blood of ischemia-modified albumin (IMA), a new biochemical marker of ischemia. When ischemia is prolonged, there will be myocardial muscle death as detected by markers of necrosis, eg, troponin I (TnI). The immediate changes in myocardial loading parameters (diastolic dysfunction) result in release of low levels of BNP, presumably directed at alleviating the ischemia. Later, in the setting of significant left ventricular (LV) systolic dysfunction, BNP levels will continue to rise. The extent to which BNP is elevated is a very good reflection of the extent of LV dysfunction at the time of measurement, thus may vary over time depending on how well the chronic heart failure is compensated. ED, emergency department; Sx, symptom.*

induced by exercise (250.5 + 142.2), compared with those who did not experience induced ischemia despite achieving similar exercise levels (124.2 + 58.6). Again, the levels of BNP resulting from exercise-induced ischemia are quite modest relative to those achieved in heart failure.[17]

BNP Levels from Acute Ischemia Versus Chronic CHF

The difference in BNP elevations seen in acute ischemia compared with those observed in chronic CHF is striking. Figure 4 compares the levels reported for mild, moderate, and severe CHF in the Breathing Not Properly Trial with those for the 25th and 75th percentile of high-risk ACS patients in the TIMI-16 (OPUS) trial. Although even the small BNP elevations seen in ACS have powerful prognostic value, it is not likely that they can be effectively used as a diagnostic marker for ischemia.

This observed difference in BNP levels must be interpreted in the context of pathophysiology: Because BNP is a counter-regulatory hormone, it is expected that its release in response to ischemia is physiologic and likely serves to induce both arterial and venous dilation as well as coronary artery dilation. All of these would act to restore a physiologic imbalance back toward homeostasis, and following this, the BNP would rapidly return to normal. It is also likely that the BNP released is from a storage pool rather than being synthesized. However, unlike atrial natriuretic peptide (ANP), which is stored in secretory granules, BNP is not stored in significant quantities within the ventricular myocardium. The parent compound, pre-pro BNP, undergoes an initial cleavage to form pro-BNP, which is released in response to increased myocardial loading and, in turn, is cleaved to form N-terminal BNP and the active carboxy-terminal BNP peptide. The fact that the quantities released in response to an ischemic event are modest might reflect the limited pool of BNP available for release, as well as the exquisite sensitivity to the hormone when receptors are relatively naïve. With ongoing stimulus for release following a large acute MI and postinfarct remodeling, clearly a change occurs in order to produce the quantities measured in the moderate to severe CHF patient. This would most certainly require an extensive capacity for de novo synthesis.

Although even the small BNP elevations seen in ACS have powerful prognostic value, it is not likely that they can be effectively used as a diagnostic marker for ischemia.

Summary

There is a dynamic relationship between the coronary arteries and the ventricles that is easily demonstrated with the counter-regulatory hormone BNP. The brief ischemia resulting from even transient coronary occlusion can cause perturbations that lead to increased release of BNP by the ventricle. BNP will dilate coronary arteries in an attempt to restore antegrade flow, thus improving oxygen delivery, and will also affect venodilation that will "unload" the ventricle and further reduce ischemia through lowering of wall tension. Thus, the low-level BNP released in response to ischemia

may well be directed primarily at the vasculature and not necessarily at the ventricle. The temporal relationship among ischemia, myocardial necrosis, and BNP is shown in Figure 5.

Following an MI, there may be extensive myocardial damage that leads to increased wall stress and a tonic release of BNP that reaches very high levels relative to those seen with ischemia. In this setting, the natriuresis/diuresis affect of BNP may be most important as this will unload the ventricle. It is not clear whether these high BNP elevations are truly physiologic, ie, are what is required for diuresis to occur. For instance, is the BNP that is released abnormal in some respect? Is there a down-regulation of the BNP receptor or its coupling mechanisms that requires substantially higher concentration to effect the required physiologic changes? These are challenging issues that are only now beginning to unfold. Although the mechanism for this disparity is unknown, it does have an impact on the utilization of BNP clinically.

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There is a dynamic interaction between the coronary arteries and ventricular function that can be demonstrated through an understanding of the physiology of the natriuretic peptides. Understanding these relationships will provide important lessons in pathophysiology, diagnosis, prognosis, and treatment for both coronary disease and CHF. ■

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Main Points

- Myocardial ischemia and infarction can manifest as both systolic and diastolic dysfunction, which emphasizes the important interaction between coronary artery disease (CAD) and left ventricular (LV) function.
- Although there has been some argument regarding which strategy is superior, it is now clear that urgent revascularization, by any means, has time-critical benefits in reducing mortality.
- A simple point-of-care assay for B-type natriuretic peptide (BNP) can rapidly and accurately identify patients with impaired LV function. This assay has proven to be of value in the emergency department diagnosis and triage of patients presenting with dyspnea because of its ability to differentiate congestive heart failure (CHF) from symptoms attributable to pulmonary etiologies.
- Both coronary artery and ventricular pathophysiology are characterized first by injury of some form, then specific functional aberrations, and then subsequent remodeling processes.
- Patients with elevated BNP at baseline had a nearly sixfold greater risk of developing heart failure (5.9% vs 1.0%, $P < .0001$) by 30 days, independent of troponin status.
- de Lemos and coworkers reported that BNP levels were higher among patients from a high-risk ACS population who had died at 30 days compared with those who were alive. The median BNP for this high-risk ACS-enriched population was almost exactly equal to the value chosen as the dichotomous cutoff by receiver-operating characteristic (ROC) analysis for a normal population.
- The observed difference in BNP levels must be interpreted in the context of pathophysiology: Because BNP is a counterregulatory hormone, it is expected that its release in response to ischemia is physiologic and likely serves to induce both arterial and venous dilation as well as coronary artery dilation.

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