THE CONCEPT OF AFTERLOAD MISMATCH AND ITS IMPLICATIONS IN THE CLINICAL ASSESSMENT OF CARDIAC CONTRACTILITY

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The characteristics of left ventricular ejection (velocity and extent of wall shortening) can be analyzed in relation to the appropriateness of the matching between afterload and the level of inotropic state (contractility), as modified by the preload (Frank-Starling) reserve. In the normal left ventricle if the preload is not allowed to compensate for an acute increase in afterload, or if the limit of preload reserve is reached, velocity ($V_{CF}$) and stroke volume will diminish; that is, an afterload mismatch occurs. This acute mismatch can be corrected by administration of a positive inotropic agent. In normal conscious animals and in man the ejection phase measures in the basal state (such as ejection fraction, and $V_{CF}$ corrected for heart size) encompass a relatively narrow range, and when the normal heart adapts successfully to a chronic pressure or volume overload such measures remain normal per unit of muscle. These findings provide the basis for their use in detecting a depressed basal level of inotropic state, even in the presence of certain valvular lesions. When there is mild depression of the basal inotropic state, enhanced preload and dilatation can allow full compensation of $V_{CF}$, but acute pressure loading can allow detection of the reduced preload reserve by inducing a substantial fall in stroke volume and $V_{CF}$. When the basal inotropic state is greatly reduced, a mismatch between afterload and contractility, expressed as reduced $V_{CF}$ or ejection function, will become evident in the basal state even if the afterload is normal. Any increase in aortic pressure will then cause a sharp reduction in stroke volume or $V_{CF}$. Also, under these circumstances therapeutic afterload reduction with agents such as nitroprusside can increase velocity and extent of wall shortening, and the cardiac output, providing the preload is maintained.

The concept of afterload mismatch with limited preload reserve provides a framework for understanding the behavior of the normal or depressed ventricle and how it can operate on a "descending limb" of function. It helps to explain why measures of the ejecting phase (which are sensitive to afterload) appear to be more reliable than isovolumic phase indices (which are relatively insensitive to afterload) for detecting depressed basal inotropic state. Finally, the concept allows for interpretation of the responses observed in the clinical setting to acute and chronic increases and decreases in loading conditions on the left ventricle.

RECENTLY, a two-dimensional framework was proposed for analysis of left ventricular function under experimental conditions and in the clinical setting which takes into account the resting fiber length (preload) and its limit of reserve, the afterload (which represents the stress

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FACTORS INFLUENCING VENTRICULAR PERFORMANCE

Fig. 1. The determinants of left ventricular performance. The mechanical determinants of cardiac performance, the preload (1) and the afterload (2), are modulated by the inotropic state (3), which shifts the function curves relating preload to the developed tension or extent of fiber shortening (short.), and the afterload to the velocity and extent of shortening. The ventricular function curves, shown at the top, relate stroke-volume (SV), stroke-work (SW), stroke-power (SP), or dp/dt to the left ventricular end-diastolic pressure (LVED) or left ventricular end-diastolic volume (LVEDV), and represent a complex expression of the curves below. The fourth determinant, heart rate, affects minute cardiac output, as well as inotropic state through the strength-interval relation.

in the left ventricular wall during systole), and the level of myocardial inotropic state. It will be the purpose of this brief review to first describe the experimental basis for describing ventricular function in terms of the matching between the level of afterload and the myocardial inotropic state, as modulated by the preload reserve, under acute and chronically altered loading conditions. The clinical implications of this construct for defining the basal inotropic state and characterizing the responses of the normal and failing human heart to altered loading conditions will then be discussed. For describing the responses of the heart to acute alterations in loading conditions or inotropic state, simple measures of performance such as the stroke volume, the left ventricular end-diastolic pressure, the systolic left ventricular or aortic pressure, can be usefully employed. The proposed framework can also be applied to analysis of cardiac adaptations over prolonged time periods and for defining ventricular function in the basal state (in comparing one heart with another, or one species with another), but for these purposes a correction must be made for heart size. Then measures of the ejecting phase such as the mean velocity of fiber shortening (mean VCF) corrected for end-diastolic diameter, the ejection fraction, or the percent shortening of the chamber diameter are employed.

Experimental Basis for the Concept
It has been shown in experimental animals that when two of the three major determinants

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Fig. 2. Relations between stroke-volume (SV) and the afterload (as reflected in the left ventricular systolic pressure, LVSPr) in four experimental animals. Each experiment is represented by a different symbol, and the left ventricular end-diastolic pressure (LVEDPr) was held constant at the level shown throughout the entire range of aortic pressures. The inverse relation between afterload and stroke-volume is evident. (Reproduced by permission from MacGregor et al., Am. J. Physiol. 227: 884–890, 1974).

Fig. 3. Changes in stroke volume (SV) and stroke work (SW), peak left ventricular pressure (LVP), and wall stress as a function of left ventricular end-diastolic pressure (LVEDP) in a dog with a mitral valve prosthesis (to prevent mitral regurgitation) during an initial afterload increase (AL) followed by rapid continuous transfusion (TRF). As the LVEDP rises beyond 32 mmHg, SV and SW decline, indicating a "descending limb" of left ventricular function. Peak wall stress continues to rise on the descending limb. (Reproduced by permission from MacGregor et al., Am. J. Physiol. 227: 884–890, 1974).

of ventricular function (preload, afterload, and inotropic state) are held constant, the third determinant can independently affect left ventricular performance (Figure 1). Indeed, the responses to alterations in these three variables are responsible for the basic function curves both of isolated cardiac muscle and the whole heart. Thus, when afterload and inotropic state are held constant, increasing preload in the isotonically contracting whole heart increases the stroke volume, the extent of wall shortening and the velocity of shortening, or augments peak tension in isometric contractions (Figure 1). When preload and inotropic state are held constant, increasing the afterload reduces the stroke volume, the extent of wall shortening, and the velocity of shortening (Figure 1). Finally, positive and negative inotropic influences shift these performance curves upward or downward, at any level of preload or afterload (Figure 1). The standard ventricular function curve in the intact animal represents a complex interaction between increasing preload and afterload as the cardiac volume is augmented by infusion, although the net effect is to increase the stroke volume, stroke work, or other measure of ventricular function (Figure 1), and this curve also is displaced by alterations in the inotropic state. Although such ventricular function curves have shown usefulness in the clinical setting their applicability is limited.

An additional important consideration in analyzing the determinants of ventricular performance is the concept of limited preload reserve. Of course, if the preload is fixed, regardless of the level of inotropic state the performance of the ejecting ventricle is inversely related to the level of afterload, as mentioned above; thus, as the aortic pressure (and hence afterload) is progressively increased, with the preload held constant at any level, the stroke
Fig. 4. Diagrammatic representation of relations between velocity of wall shortening (VCF) and afterload or wall stress. (Under acutely changing conditions systolic aortic pressure and stroke volume (SV) can be used).

The group of curves in the center represents the normal level of inotropic state and shows progressive increases in preload up to the limit of the preload (Frank-Starling) reserve. Point A represents the basal level of inotropic state; with modest afterload increase, no change in mean VCF occurs because of preload compensation, but with a severe afterload increase a mismatch occurs and mean VCF or stroke-volume fall (point B) as the limit of preload reserve is reached and exceeded (dashed arrow). The dashed force-velocity curve to the right indicates that administration of a positive inotropic agent will increase the preload reserve and also allow more shortening and higher velocity at any level of afterload (point C).

The lower group of curves (failure) represents severe depression of the basal inotropic state. Point D represents the resting state which is depressed compared to A, and in which the preload reserve is already fully utilized. Under these conditions any increase in the afterload results in a depression of stroke-volume or mean VCF (point E). If the afterload is reduced, and preload is sufficiently well maintained (point F) stroke-volume and mean VCF will increase. However, if the preload is allowed to fall substantially as the afterload is reduced, no change or even a fall in these measures may occur (point G).

Volume will progressively fall (Figure 2) along with the velocity of ejection, the extent of wall shortening, and the ejection fraction. This response is, in fact, the basic expression of the force-velocity-length relation. However, if the preload is allowed to compensate as the aortic pressure is augmented, provided the venous return is adequate the stroke volume will tend to be maintained or to fall only slightly over a moderate range of aortic pressures. If the preload is progressively increased by a rapid venous infusion at a moderately elevated aortic pressure in an open-chest dog preparation, when the average left ventricular end-diastolic pressure exceeds 30 mmHg continued volume loading results in a decrease in stroke volume and stroke work, an apparent “descending limb” of performance. This occurs even when mitral regurgitation is excluded by replacement of the mitral valve with a caged-ball prosthesis, stroke volume and stroke work declining when the left ventricular end-diastolic pressures exceeds 30 mmHg (Figure 3). However, at such elevated filling pressures, left ventricular systolic pressure and calculated wall stress always increased somewhat further as the descending limb of function occurred (Figure 3), and further increases in aortic pressure caused a striking reduction in stroke volume and stroke work. Therefore, when diastolic fiber length is held constant or when the limit of preload reserve is reached, left ventricular performance becomes inversely related to the ventricular volume and the systolic pressure, i.e., to the afterload. Stated another way, once the ventricle reaches the limit of preload reserve at a given level of inotropic state, any further increase in afterload forces it to move down a force-velocity curve, a situation which may be
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normal limits; the extent of shortening of the internal diameter as well as the stroke-volume also tend to fall somewhat as the systolic pressure reaches high levels (Figure 5). However, if such a phenylephrine infusion is repeated during isoproterenol infusion, while there is a mild initial fall in mean V CF (perhaps due to reflex withdrawal of sympathetic tone or to inadequate venous return), as end-diastolic pressure and afterload are then increased further there is little change in mean V CF, and no reduction in the extent of shortening or the stroke-volume occurs throughout the full range of aortic pressures (Figure 5).8 Thus, a mild afterload mismatch which was evident under control conditions did not occur at the higher levels of inotropic state produced by isoproterenol infusion, presumably because reduced cardiac size could increase the preload reserve, and also because the shift of the force-velocity and force-shortening relations lead to a stronger and faster ventricle at any level of afterloading. This response is shown diagrammatically in Figure 4.

These findings serve to support the view that the characteristics of left ventricular ejection represent the appropriateness of the matching between the level of afterload and the existing inotropic state, as modified by the venous return and the preload reserve. It might further be expected, as discussed subsequently, that depression of the inotropic state would reduce the preload reserve, as well as the ability of the ventricle to shorten against a given afterload.

Ventricular Ejection Characteristics in the Basal State

Conscious resting animals and normal human subjects in the basal, resting state exhibit a relatively predictable range for measures of the ejection phase of left ventricular contraction, when they are expressed in terms of function per unit of ventricular circumference or force per unit cross sectional area of the wall.2,3 Although a single point on the force-velocity relation in man can be analyzed,9 it was later found empirically that measures such as the mean V CF normalized to end-diastolic circumference, the ejection fraction, and the mean normalized systolic ejection rate themselves exhibit a reproducible range in dogs8 and in normal human subjects10 Therefore, for the purpose of comparing normal and diseased hearts in the basal state, reductions in these measures alone can detect depressed inotropic state, often without the need for

defined as an afterload mismatch (Figure 4).4

The level of inotropic state, of course, determines the response to a given afterload, and also influences the preload reserve. Studies in the conscious dog8 have shown that when the afterload is increased by progressive infusion of a pressor agent (phenylephrine) at a constant paced heart rate, as the left ventricular end-diastolic pressure rises there is some fall in mean V CF, even though this tends to remain within

Fig.5. Study in a conscious, chronically instrumented dog showing the responses to a progressive acute pressure overload, the increases in left ventricular systolic pressure (LVSP) being induced by infusion of phenylephrine. Heart rate (HR) was controlled by atrial pacing. ΔLV = excursion of the left ventricular minor equator measured by implanted miniature ultrasonic crystals; LVEDD=left ventricular end-diastolic diameter; LVEDP=left ventricular end-diastolic pressure.

It is evident that with pressure loading during isoproterenol infusion, extent and velocity of shortening are maintained at higher levels than with pressure loading under control conditions. ΔLV = shows no change during pressure loading after isoproterenol and after an initial fall mean V CF is maintained relatively constant as well. For further discussion see text. (Reproduced by permission from Mahler et al., Am. J. Cardiol. 35: 626–634, 1975).

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Fig. 6. Responses to chronic volume overloading in conscious dogs induced by means of a large arterio-venous fistula. The average changes in the percent shortening of the minor equator of the left ventricle and in the circumferential fiber shortening rate (mean VCF, in end-diastolic circumferences/sec.) are shown. Measurements early post shunt (EPS) at about one week, and late (LPS) at about ten weeks after creation of the shunt are shown, together with the standard errors of the mean. Measurements in a single dog that developed severe congestive heart failure (CHF) are also shown. NS = no significant difference. (Reproduced by permission from Ross and McCullagh, Circ. Res. 30: 549–556, 1972).
Fig. 7. Summary of responses to severe chronic volume overloading, produced in the dog by a large infrarenal arterio-venous fistula. Afterload is shown on the abscissa, and the mean velocity of fiber shortening (V_{CF}) corrected for end-diastolic diameter is shown on the ordinate.

Panel A: The responses to acute severe volume overloading are indicated. The diagrams represent a cross-sectional view of the left ventricle, showing changes in chamber diameter and wall thickness. With marked acute volume overloading, the left ventricular chamber dilates, the wall thinning and increased chamber size tending to increase the afterload, but through use of the preload reserve mean V_{CF} remains relatively constant (point A to B).

Panel B: During the weeks after imposition of the volume overload, the ventricle remains at or near the limit of the preload reserve, i.e., there is near maximum use of the Frank-Starling mechanism. However, the chamber shows progressive eccentric hypertrophy with dilatation and the wall thickens to some degree (points B to C). This adaptation allows delivery of a much larger stroke-volume, but when corrected for chamber diameter and alterations in muscle mass, the force-velocity relation as reflected in the mean V_{CF} remains normal, indicating a normal level of inotropic state (point C).

equator were within normal limits and showed no detectable change between early and late studies (Figure 6); however, in one animal that developed severe cardiac failure these values were markedly reduced (Figure 6). When these results are considered in concert with other experimental observations which showed no increase in midwall sarcomere lengths in chronically volume overloaded left ventricles beyond that observed with acute volume overloading (about 2.2 μm), it is evident that by a change in geometry and increased number of sarcomeres the left ventricle can augment its performance during chronic progressive dilatation without further use of the Frank-Starling mechanism (at the ultrastructural level) beyond that used acutely, and at a normal level of inotropic state. Therefore, the enhancement of overall cardiac performance during chronic volume overloading appears to be mediated through normal performance of each unit of an enlarged circumference operating at an optimal, elongated sarcomere length.

These responses are summarized diagrammatically in Figure 7. The initial response to creation of the large volume overload consists of near-maximum use of the Frank-Starling mechanism. Because the preload is increased, the somewhat increased afterload (produced by increased heart size and decreased wall thickness) does not result in a fall of mean V_{CF}, and no afterload mismatch occurs. The main adaptation occurs over many weeks as eccentric hypertrophy takes place, more sarcomeres and myocardial tissue being generated in series, with only a mild increase in wall thickness; during this adaptation, maximum use of the Frank-Starling mechanism tends to be maintained (Figure 7). As the heart enlarges, however, the ventricle is able to deliver a much larger stroke-volume, but with a normal extent of wall shortening per unit of circumference; the normal V_{CF} further indicates that the inotropic state remains normal.

Adaptations to Chronic Pressure Overloading:
Fig. 8. Responses to chronic supravalvular aortic constriction in dogs chronically instrumented with ultrasonic crystals for measurement of left ventricular dimensions.

Left Panel: The average change from control of left ventricular systolic pressure ($\Delta$LVSP) immediately (acute), early (average 9 days) and late (average 2 1/2 weeks) after aortic constriction; the responses immediately (acute) and 24 hours after release of the constriction also are shown. The change in the cross-sectional area (CSA) of the left ventricular wall, calculated from the measured wall thickness and the chamber diameter, is shown below.

Middle panel: Changes in left ventricular end-diastolic diameter from control ($\Delta$EDD); it may be noted that during the late adaptation the EDD returns to control. The change in the percent shortening of the minor equator is shown below, a marked decrease occurring acutely returns to control in the compensated late stage of aortic constriction.

Right panel: Force-velocity relations as reflected by change from control of peak wall stress (WSf) and corrected mean velocity of internal diameter shortening (mean Vf). As the ventricle accommodates to the pressure overload, velocity of shortening returns to normal as wall thickening accomplishes a decrease in wall stress. Following relief of the aortic constriction there is a tendency toward increased velocity at a somewhat reduced wall stress, but these changes are not statistically significantly (NS) different from control. (Reproduced by permission from Sasayama et al., Circ. Res. 38: 172–178, 1976.)
Fig. 9. Summary of responses to severe chronic pressure overload in the dog subjected to supravalvular aortic constriction. As in Figure 7, afterload and corrected velocity of wall shortening (mean $V_{\text{CF}}$) are as shown together with a cross sectional diagram of the left ventricle.

**Panel A:** The acute responses to severe pressure overload consist of initial use of the Frank-Starling mechanism as the normal ventricle (point A) moves out to the limit of the preload reserve; this reserve is then exceeded, and the ventricle moves down a force-velocity relation as chamber dilatation, wall thinning, and increased systolic pressure cause a marked increase in the afterload. As this occurs $V_{\text{CF}}$ falls (point B).

**Panel B:** Over the ensuing weeks, the chronic adaptation consists of concentric left ventricular hypertrophy (point B to C). As shown at point C, the internal left ventricular diameter returns to normal and the wall thickness increases markedly. This adaptation returns the ventricle to the control force-velocity curve, but now the afterload is normal because a markedly increased left ventricular wall thickness has returned the wall force to normal per unit cross sectional area. Since the afterload has returned to normal, the $V_{\text{CF}}$ also becomes normal. This response is shown by the simplified Laplace equation for wall tension shown below the diagram of the left ventricle. The markedly increased systolic pressure (P) in the left ventricle due to the supravalvular constriction is compensated for by the large increase in wall thickness (h), radius (r) having returned to normal.

The responses to chronic pressure overloading have been studied in a conscious, chronic canine model in which an implanted pneumatic cuff is inflated around the ascending aorta. The dogs were also instrumented with intraventricular micromanometers, and pairs of ultrasonic crystals for the measurement of wall thickness and internal left ventricular chamber diameter. During initial inflation of the cuff to produce left ventricular pressures averaging 220 mmHg, calculated peak wall stress increased by more than 50%, while mean shortening velocity ($V_{\text{CF}}$) decreased by 40% (Figure 8). As concentric hypertrophy developed over the ensuing two to three weeks, wall thickness increased and wall stress fell toward control, while end-diastolic diameter, percent shortening, and mean $V_{\text{CF}}$ returned to control (Figure 8). Twenty-four hours after release of the cuff, these values (as well as peak dp/dt) were not significantly different from control. Thus, the left ventricle responded to chronic pressure overload by initial dilatation with markedly increased wall stress, followed by gradual wall thickening and consequent reduction of wall stress to near normal levels. There was no evidence that hypertrophy produced intrinsic depression of the myocardial inotropic state.

The responses to sustained chronic pressure overloading are summarized diagrammatically in Figure 9. Acute severe pressure overloading produces an acute afterload mismatch, the level of inotropic state and the available mass of the myocardium being insufficient to sustain shortening. Thus, the markedly increased systolic pressure together with wall thinning produce a large increase in the systolic wall stress (afterload) and extent of shortening and $V_{\text{CF}}$. 

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fall (Figure 9). It is also possible that subendocardial ischemia could have contributed to this change by shifting the force-velocity curve somewhat to the left under these acute conditions, although the initial responses occurred within a few beats and would appear to be too rapid for this to be the major explanation. Subsequently, with concentric hypertrophy of the ventricle the chamber returns to normal size, and (as reflected in the simplified equation for wall stress shown in Figure 9) this change together with the increased wall thickness returns the afterload to normal, despite a sustained elevation of systolic ventricular pressure. Thus, without a change in inotropic state, concentric hypertrophy allows correction of the early afterload mismatch and allows a normal $V_{CF}$ and extent of shortening (corrected to per unit circumference) without encroachment upon the preload reserve (Figure 9).

**Afterload Mismatch in the Clinical Setting**

Under normal conditions the human left ventricle exhibits a relatively narrow range of values of ejection phase measures, and in the basal resting state the level of venous return and the preload can be considered non-limiting; by definition, the normal level of afterload is appropriately matched to the normal level of basal inotropic state (Figure 4). Only mild changes in stroke-volume or $V_{CF}$ appear to occur in normal man in response to a moderate acute pressor stress with phenylephrine, angiotensin, or to phenylephrine in the conscious dog as described earlier (Figure 5). When the inotropic state is mildly reduced, encroachment upon the preload reserve can allow maintenance of normal stroke volume and $V_{CF}$ at rest. However, since the preload reserve has been partly utilized, a significant reduction in stroke-volume or $V_{CF}$, to below the normal range, might be expected with elevation of the afterload. Thus, as we described with infusion of angiotensin acute pressure loading can allow detection of mild depression of the inotropic state, probably by inducing an afterload mismatch.

When the basal inotropic state is substantially reduced, a mismatch between the level of inotropic state and the afterload can exist in the resting state, even if the aortic pressure and the afterload are normal. This mismatch will then be expressed as a reduced basal $V_{CF}$ or ejection fraction (Figure 4). Under these conditions, there may be no preload reserve, and any degree of aortic pressure elevation will cause a very sharp reduction in stroke-volume and $V_{CF}$ (Figure 4). This type of response in the stroke volume also was described in patients with dilated hearts during angiotensin infusion.

Acute, severe mitral regurgitation or sudden severe aortic regurgitation, as in infective endocarditis, can result in a severe reduction of left ventricular performance. This response may be due, in part, to subendocardial ischemia or other myocardial damage; however, it also seems likely that the preload reserve is exceeded with such severe volume overloading, and under these circumstances cardiac dilatation with wall thinning, together with some increase in systolic pressure could lead to an afterload mismatch (Figure 3). This can be partially corrected by use of a positive inotropic agent and/or vasodilator therapy, or reversed by correction of the valvular leak by means of valve replacement. The left ventricle also can be faced with an acute, severe pressure overload in malignant hypertension; the severe left ventricular dysfunction and failure produced by the acute afterload mismatch (Figure 9A) in such hypertensive crises can be corrected by rapid reduction of the aortic pressure.

Under conditions where very marked depression of inotropic state exists, such as in cardiogenic shock after acute myocardial infarction, an afterload mismatch may exist at any level of aortic pressure. Under these conditions, reduction of the afterload by such measures as intraaortic balloon counterpulsation can cause a substantial decrease in afterload, and improvement in ejection characteristics and cardiac output. In addition, therapeutic afterload reduction by vasodilating agents such as nitroprusside or nitroglycerin can increase the velocity and extent of wall shortening (Figure 4). It is also evident, however, that with such therapeutic afterload reduction, performance can be increased only if preload is adequately maintained, since if preload is allowed to fall substantially, stroke-volume and performance may be unchanged or actually diminish (Figure 4).

**Other Implications**

The idea of limited preload reserve and afterload mismatch provides a framework for understanding the behavior of the normal or depressed human ventricle under various abnormal loading conditions and helps to explain how the ventricle can operate on a “descending limb” of function.
In addition, the concept offers a possible explanation of why measures of the ejecting phase (such as mean $V_{CF}$ and the ejection fraction) appear to be more reliable than the isovolumic phase indices for detecting depressed basal inotropic state. The explanation may well relate to the fact that the ejecting phase measures are sensitive to afterload, whereas the isovolumetric phase indices ($dp/dt$; $dp/dt/P$; “Vmax”) are not; therefore, the latter may be unable to detect the afterload mismatch which exists in the depressed heart. One note of caution should be mentioned relative to severe mitral regurgitation associated with marked depression of myocardial inotropic state; under these circumstances, mean $V_{CF}$ and the ejection fraction may be maintained at higher levels than the myocardial disease per se would dictate because of the relatively low afterload on the left ventricle afforded by the low impedance regurgitant leak. Finally, the approach described allows for an interpretation of the responses observed in the clinical setting to inotropic agents, or to therapeutic reductions in afterload produced by counterpulsation or vasodilating agents.

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