Vasodilator Therapy for Heart Failure
The Influence of Impedance on Left Ventricular Performance

The role of the arterial system in determining the performance of the diseased left ventricle has been relatively neglected in traditional thinking about heart failure. Attention has instead been focused on the influence of diastolic filling of the ventricle and of its contractile state. Therapy directed at altering these latter factors in cardiac performance has served as the cornerstone of the management of congestive heart failure. However, recent studies have demonstrated dramatic hemodynamic improvement during administration of vasodilator drugs in patients with left ventricular failure due to acute myocardial infarction, chronic ischemic heart disease, and cardiomyopathy. An understanding of this response requires consideration of the concept of impedance to left ventricular outflow.

During ventricular systole the rise in aortic pressure is related to the stroke volume, its rate of ejection, and the impedance the blood faces as it crosses the aortic valve. Changes in total impedance during ejection are due to alterations in either the compliant component, which opposes a change in volume of the arterial vascular bed, or the resistive component, which opposes runoff of blood from the arterial tree and is determined primarily by the cross-sectional area of the arterioles and the viscosity of blood. If impedance increases because of arteriolar vasoconstriction or reduced arterial compliance, then aortic systolic pressure will rise more rapidly with any given ejection rate, and mean left ventricular systolic pressure will be increased for any given stroke volume. During ejection the rise in left ventricular pressure is accompanied by a reduction in left ventricular chamber size so that wall tension (pressure × radius) normally tends to fall during systole. When impedance is increased, a greater rise in pressure for any given reduction in chamber size means that left ventricular wall tension during systole will be higher. Since wall tension is an important determinant of myocardial oxygen consumption, the greater the impedance the higher the ratio between oxygen cost and stroke volume. This ratio is further increased when the ventricle is dilated, since under these circumstances radius is reduced less during systole for any stroke volume.

An increased impedance to left ventricular ejection will not necessarily alter stroke volume when the heart is normal. Despite an increment in systolic ventricular wall tension (afterload), normal fiber shortening is accomplished primarily by an unexplained compensatory increase in myocardial contractility referred to by Sarnoff as homeometric autoregulation. When left ventricular function is impaired, however, increases in impedance are not tolerated with such impunity. The reserve capacity of the diseased ventricle is limited, and the increased afterload precipitates a reduction of fiber shortening and ejection fraction. A rise in left ventricular end-diastolic pressure may reflect a compensatory increase in end-diastolic fiber length (Frank-Starling mechanism), which tends to support stroke volume. This abnormal increase in ventricular filling pressure serves as the basis for angiotensin infusion and isometric hand grip as tests of subclinical ventricular dysfunction. The abnormal ventricle faced with heightened impedance therefore exhibits an increased ventricular volume and pressure with a reduced ejection fraction resulting in the consumption of more oxygen to deliver a smaller stroke volume.

A high impedance during left ventricular outflow is characteristic of clinical heart failure. Arteriolar vasoconstriction may result from reflex activation of the sympathetic nervous system or the release of renin or other humoral vasoconstrictor substances. An increase in sodium and water content of vessel walls and an increase in interstitial volume and pressure also may reduce cross-sectional area of the vascular bed and increase both the resistive and...
compliant components of impedance. In addition, a reduction of flow velocity in the microcirculation increases the viscosity of blood and may contribute to a further rise in resistive impedance. When the heart is normal and stroke volume falls because of a primary reduction in venous return, an increase in peripheral resistance serves as an appropriate compensatory mechanism by which aortic pressure is supported. However, when stroke volume falls because of cardiac impairment, a rise in resistance may be detrimental. The cerebral and coronary circulations may be protected from the lethal effects of hypotension, but the increase in impedance may further decompensate the failing left ventricle. Unfortunately, the impedance is not precisely set at the minimum level necessary to maintain effective perfusion pressure. Indeed, the reflex response of the peripheral vascular bed may be so exaggerated that arterial pressure rises above control levels despite a considerable reduction in cardiac output. Thus the diseased ventricle is asked to generate a normal or greater than normal systolic wall tension at a time when its contractile force is impaired and a lower than normal arterial pressure would be better tolerated. The result may be a further reduction in ejection fraction and stroke volume which could initiate a vicious cycle characterized by a progressive reduction in cardiac output and a progressive increase in impedance. If sodium retention, reflex cardiac stimulation, and other negative feedback loops succeed in stabilizing the cardiac output, a state of chronic heart failure will exist; continuation of the vicious cycle may eventuate in the syndrome of shock.

A variety of vasodilator agents have been demonstrated to reverse some of the hemodynamic abnormalities of heart failure. Acute administration of sodium nitroprusside, phenolamine or nitroglycerin results in a sharp reduction in left ventricular filling pressure and an increase in cardiac output. The magnitude of the rise in cardiac output tends to be directly related to the degree of its initial depression. When the output is normal, as in some patients with acute myocardial infarction, little change occurs during vasodilator therapy. On the other hand, when cardiac output is markedly depressed, it may be increased to normal levels during treatment. In a series of patients with chronic intractable low output heart failure due to coronary artery disease or cardiomyopathy who were treated with intravenous sodium nitroprusside, cardiac output was nearly doubled, urine flow increased and the signs and symptoms of heart failure were relieved. The increase in stroke volume which accompanies vasodilator therapy tends to counterbalance the fall in systemic vascular resistance so that the reduction in mean arterial pressure is surprisingly small, and in some patients pressure recovers to pretreatment levels during continuous therapy. Thus a new steady state may be generated in which cardiac output is higher and impedance lower at nearly the same arterial pressure. Furthermore, heart rate usually does not rise but instead may fall as a manifestation of the circulatory improvement. The heart rate response may depend on the vasodilator drug employed, although definitive data on this point are not yet available.

The fall in left ventricular filling pressure which accompanies the vasodilator effect in heart failure requires closer scrutiny. Some of this response could represent an increase in ventricular compliance, but it also is likely that ventricular end-diastolic volume falls, at least in patients with markedly dilated hearts. A decrease in left ventricular end-diastolic volume could represent the combined effect of an increased ejection fraction and some venous pooling because of dilation of the capacitance vessels. Indeed, it might be attractive to postulate that the augmentation of stroke volume is due at least in part to improved ventricular function resulting from a reduction of preload in the overstretched ventricle which might be operating on a "descending limb" of its Starling curve. However, it is unlikely that a reduction in preload is an important primary factor in the acute increase in stroke volume since comparable reductions in left ventricular filling pressure induced by venous occluding tourniquets or phlebotomy lowered cardiac output in the same patients in whom nitroprusside infusion increased it. Although a fall in ventricular preload certainly may have a salutary long-term effect on cardiac function, the immediate improvement in left ventricular performance probably must be attributed largely to a reduction in impedance to ejection.

Although individual vasodilator drugs may have unique circulatory effects, they all relax vascular smooth muscle. A reduction of arteriolar resistance will allow more rapid runoff from the arterial bed during systole (reduced resistive impedance) whereas relaxation of the smooth muscle in the larger arteries may modify their pressure-volume relationship (reduced compliant impedance). Furthermore, as described above, these agents also may dilate venous capacitance vessels. Coronary
vasodilation induced by some of the drugs could
contribute to improved myocardial function, but
since a similar hemodynamic response is observed
in both ischemic and nonischemic heart disease, it is
unlikely that improved coronary perfusion plays a
dominant role in the immediate circulatory response
to vasodilators.

The effect of vasodilator therapy on cardiac
metabolism is more complex. A reduction in left
ventricular volume at end-diastole, and particularly
during systole, along with some reduction in systolic
pressure, signifies a considerable fall in myocardial
oxygen consumption. The oxygen cost to stroke
volume ratio therefore should be markedly lowered.
This reduction in myocardial oxygen needs could be
particularly beneficial in acute myocardial infarction
and ischemic heart disease, in which an
imbalance between oxygen supply and demand
may directly impair cardiac function. However, net
improvement in myocardial metabolism depends on
the balance between changes in myocardial oxygen
delivery and oxygen consumption. A reflex increase
in heart rate, as has been reported in some patients
given phentolamine,14 could increase oxygen con-
sumption and aggravate ischemia. The fall in aortic
diastolic pressure during vasodilator therapy, even
if small, could reduce coronary blood flow. Regard-
less of changes in total coronary flow, however,
subendocardial perfusion might be fa-
vored by a fall in the elevated left ventricular
diastolic pressure which directly inhibits subendo-
cardial flow.17 Nonetheless, recent studies have
suggested that the salutary effect of nitroglycerin on
myocardial ischemia in experimental myocardial
infarction can be enhanced by maintaining a
constant aortic pressure.18 Thus, it is premature to
determine whether pharmacological reduction of
impedance in patients with acute myocardial
infarction will have a net beneficial effect, even if
arterial pressure falls slightly, or whether it is vital
to maintain, or even increase coronary perfusion
pressure by use of intraaortic balloon or external
counterpulsation.19

Data are not yet available to provide a
comparison between the effects of conventional
therapy (diuretics and inotropic drugs) and the
effects of pharmacological reduction of impedance
on the signs and symptoms of heart failure. Studies
reported to date have been limited to intravenous
administration of drugs for periods not exceeding
72 hours. The efficacy of long-term therapy would
be considerably more difficult to demonstrate, but
such studies eventually must be undertaken. Chron-
ic treatment would require the development of a
well-tolerated, potent, orally effective vasodilator
which does not induce a reflex tachycardia. It is
likely that a variety of chemical agents which might
meet these requirements could be synthesized.
Furthermore, it would be beneficial if the peripheral
vasodilator action resulted in distribution of the
increased blood flow to critical vascular beds which
previously were underperfused.

The impressive preliminary results with vasodila-
tor therapy in heart failure of diverse etiologies
suggests that hypertension is a more important
factor in cardiac decompensation than was previ-
ously recognized. Data from the Framingham study
have revealed that hypertension is the most
common risk factor in the development of heart
failure.20 Indeed, the systolic pressure, which is a
resultant of impedance to ejection, was more closely
related with subsequent heart failure than the
diastolic pressure. It may therefore be appropriate
to consider arterial systolic pressure the vital
variable in circulatory homeostasis. Marked eleva-
tions of arterial pressure due to high impedance
can decompensate a mildly abnormal heart, as in
hypertensive crisis,21 but modest increases in
pressure or even normal pressures may precipitate
clinical heart failure when the ventricle is ischemic
or its function severely compromised. Further
experience may considerably expand the already
broad application of antihypertensive therapy in
our adult population.19, 22

JAY N. COHN

References
1. FRANCIOSA JA, GUIHA NH, LIMAS CJ, RODRIGUEIRA E,
COHN JN: Improved left ventricular function during
nitroprusside infusion in acute myocardial infarction.
Lancet 1:650, 1972
2. MAJID PA, SHARMA B, TAYLOR SH: Phentolamine for
vasodilator treatment of severe heart-failure. Lancet
2:719, 1971
3. GUIHA NH, LIMAS CJ, FRANCIOSA JA, COHN JN:
Treatment of refractory heart failure with sodium
nitroprusside. Circulation 46 (suppl 2): II-105,
1972
4. GOLD HK, LEINBACH RC, SANDERS CA: Use of
sublingual nitroglycerin in congestive failure follow-
ing acute myocardial infarction. Circulation 46:839,
1972
5. SANDLER H, DODGE HJ: Left ventricular tension and
6. SONNENBLICK EH, SKELTON CL: Myocardial energet-
ics: Basic principles and clinical implications. N Eng
7. BURTON AC: The importance of the shape and size of
the heart. Amer Heart J 54:801, 1957

Circulation, Volume XLVIII, July 1973
9. Ross J Jr, Braunwald E: The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin. Circulation 29: 739, 1964
Vasodilator Therapy for Heart Failure: The Influence of Impedance on Left Ventricular Performance

JAY N. COHN

Circulation. 1973;48:5-8
doi: 10.1161/01.CIR.48.1.5

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1973 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/48/1/5.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/