Mitogen-Activated Protein Kinases as Biomarkers of Hypertension or Cardiac Pressure Overload

María P. Ocaranza, Jorge E. Jalil

In hypertension, left ventricular hypertrophy is initially a useful compensatory process that represents an adaptation to increased ventricular wall stress. It is also one of the first steps toward overt clinical disease. Several changes in myocardial structure characterize hypertensive or pressure-overload heart disease that induces myocardial remodeling (eg, enhanced cardiomyocyte growth, excessive cardiomyocyte necrosis/apoptosis, accumulation of interstitial and perivascular collagen fibers, or disruption of the endomyrial and perimysial collagen network). In the long term, these cellular changes, if untreated, will deteriorate left ventricular function and facilitate the development of heart failure.

The growth and survival of adult cardiomyocytes, smooth muscle cells, and macrophages are regulated by extracellular ligands, growth factors, and cytokines that bind to cell-surface receptors and activate intracellular signal transduction cascades. These signaling pathways control essential processes in all eukaryotic cells, including gene transcription, protein translation, cytoskeletal remodeling, endocytosis, cell metabolism, cell proliferation, and survival. One of the best-described signal transmission systems activated by pressure overload involves multiple cascades of protein phosphorylation by the mitogen activated protein kinase (MAPK) family, with diverse roles in a broad range of physiological functions. The MAPK signaling pathway sequences ultimately in the dual phosphorylation and activation of terminal kinases, such as p38, c-Jun N-terminal kinases (JNKs), and extracellular signal-regulated kinases (ERK1/2 and ERK5), which are involved in different cellular responses, including pressure-overload–induced cardiac hypertrophy. MAPK cascades are triple-kinase pathways that include an MAPK kinase kinase, an MAPK kinase, and a terminal MAPK. MAPK cascades may be organized in this fashion to promote signal amplification and fidelity.

The MAPK signaling cascade (see Figure) is initiated in cardiac myocytes by ligand-receptor interactions, such as G protein–coupled receptors (angiotensin II, endothelin 1, and adrenergic receptors), receptor tyrosine kinases (insulin growth factor 1 and fibroblast growth factor receptors), receptor serine/threonine kinases (transforming growth factor-β), cardiotrophin 1 (gp130 receptor), and also by stress stimuli, such as stretch. Cardiac myocytes directly detect mechanical deformation or stretch through an internal sensory apparatus. One such apparatus might involve integrins that link the extracellular matrix to the intracellular cytoskeleton. In this regard, the integrin-interacting molecule melusin has been implicated as a sensor of mechanical stress in cardiac myocytes. A second sensing apparatus has been proposed at the level of the Z-disc within each sarcomere. Biomechanical stress can also be transduced at the cell membrane independently of structural proteins. For example, the angiotensin II type 1 receptor directly associates with Janus kinase 2 and induces the translocation of G proteins into the cytosol on stretch, leading to ERK activation and hypertrophy.

The identification of biomarkers of potential usefulness for the correlation between the amount of pressure overload and the cardiac stress evolving to heart failure has been a prolific field in the last years.

To identify possible surrogate markers capable of detecting increased pressure overload and left ventricular hypertrophy development, Esposito et al assayed the activity (phosphorylation levels) of ERK, JNK, and p38 in aortic banded mice. In this model, increased cardiac mass was proportional to the amount of pressure overload, and a significant linear correlation was observed among the 3 MAPK activations and pressure overload. Importantly, ERK, JNK, and p38 activation in left ventricular samples and white blood cells (WBCs) were correlated. No correlation was found between atrial natriuretic factor mRNA levels and hypertrophy.

In a second set of measurements in humans, they tested whether ERK activation might reflect uncontrolled blood pressure levels. They assayed ERK phosphorylation in WBCs from normotensive volunteers, hypertensive patients with controlled blood pressure values, or hypertensive patients with uncontrolled blood pressure values (systolic blood pressure: >150 mm Hg). ERK phosphorylation in isolated leukocytes was increased in hypertensive patients with uncontrolled blood pressure values compared with normotensive volunteers. In hypertensive patients with controlled blood pressure values, ERK phosphorylation and left ventricular mass were significantly reduced compared with hypertensive patients with uncontrolled blood pressure values. In the hypertensive patients, JNK phosphorylation was higher and similar in hypertensive patients with controlled blood pressure values and hypertensive patients with uncontrolled blood pressure values compared with normotensive volunteers, and p38 activation was not observed. Levels of inflammation (both in mice and in humans), as well as urinary catecholamine levels, in humans were similar in all of the groups. Their results suggest the following: (1) in mice, ERK, JNK,
and p38 activation in peripheral WBCs are closely correlated with pressure overload; (2) in patients, ERK activation in WBCs reflects the degree of hypertension control; and (3) leukocytes might represent important cellular targets to mirror cardiac signaling.6

For a circulating molecule to be considered a biochemical marker of myocardial remodeling, and possibly of cardiac overload, some criteria have been proposed recently by the Gonzalez et al.1 The criteria are as follows: (1) a relationship between its expression in the myocardium and its blood concentration; (2) a positive gradient from its concentration in coronary sinus blood toward its concentration in peripheral vein blood, proving its main cardiac origin; (3) an association between its blood concentration with the cardiac structural and/or functional parameters reflecting the hallmarks of the myocardial changes under study1; and (4) levels that vary in parallel with the changes in the above parameters induced by pharmacological treatment. In addition, its determination must be easy and reproducible, and the biochemical marker must have a good sensitivity and specificity to detect the pathology under study.1 In hypertensive patients, some new biomarkers are promising in terms of their clinical perspectives (Table).

Although ERK phosphorylation in WBCs is not exactly a molecule produced in the heart and assayed in the circulation, the current data of Esposito et al6 meet with almost all of the

Table. Current Biomarkers in Hypertensive Patients1,7

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Pathological Significance</th>
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<tbody>
<tr>
<td>Cardiotrophin 1</td>
<td>Left ventricular hypertrophy</td>
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<tr>
<td>Annexin A5</td>
<td>Apoptosis-related cardiomyocyte dysfunction (deterioration of cardiac pump performance)</td>
</tr>
<tr>
<td>Carboxy-terminal propeptide of procollagen type 1</td>
<td>Collagen type 1–dependent myocardial fibrosis</td>
</tr>
<tr>
<td>Metalloproteinase 1:TIMP-1 ratio</td>
<td>Altered collagen network (left ventricular dilatation and systolic dysfunction)</td>
</tr>
<tr>
<td>Metalloproteinase 9</td>
<td>Blood pressure progression on follow-up</td>
</tr>
</tbody>
</table>

Data adapted from references 1 and 7. TIMP indicates tissue inhibitor of metalloproteinases 1.
above criteria and might have high potential clinical relevance. Serial changes with hypertension treatment, as well as reproducibility, must be tested before ERK activity in WBCs can be considered a true new biomarker of hypertension control or of cardiac pressure overload. In addition, these data raise very fundamental questions that must be addressed in future studies concerning the mechanisms responsible for the MAPK pathway activation in WBCs either in mice or in patients and also regarding how blood pressure overload, per se, might activate this signaling pathways in WBCs as it does in the heart.

Sources of Funding
This work was supported by Fondo Nacional de Desarrollo Científico y Tecnológico (Fondecyt) grants 1085208 and 1070662.

Disclosures
None.

References
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_Hypertension._ 2010;55:23-25; originally published online November 9, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.141960

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

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