Raised Diastolic Pressure as an Early Predictor of Left Ventricular Remodeling After Infarction: Should Echocardiography or Natriuretic Peptides Be Used for Assessment?

Frank A. Flachskampf

Medizinische Klinik 2, University of Erlangen, Erlangen, Germany

“Risk” after myocardial infarction classically means risk of cardiac death or re-infarction; other adverse events can be included in the end-point such as hospitalization due to recurrent ischemia, new atrial fibrillation, embolic events, and others. However, the most important adverse “event” next to death and re-infarction is the development of heart failure. In this context, risk stratification has become a buzzword in clinical cardiology, serving as a justification for a bewildering array of tests creating a multitude of parameters, from ejection fraction to late ECG potentials to biomarkers, which all compete for the clinicians’ attention and the health system’s resources. However, risk stratification alone does not reduce mortality or morbidity; it is worthwhile doing it only if it helps to tailor therapeutic and preventive management to the individual patient.

After myocardial infarction, the left ventricle develops a set of morphologic and functional responses to the initial ischemic injury that have been labelled as post-infarction remodelling. In this process, the infarcted area initially bulges and expands within seconds of the onset of coronary occlusion. During the ensuing hours and days, the infarct scar is stretched, thereby increasing in size; this process has been termed infarct expansion. In response to a substantial loss of contractile tissue, the left ventricle acutely responds by hyperkinesia of remote myocardial areas and in the course of days and weeks dilates, thus recruiting preload reserve.

These changes are compounded by the development of mitral regurgitation due to ventricular dilatation and accompanied by complex biochemical and neuro-endocrine alterations. Although remodelling is most pronounced after large infarcts, it is difficult to pinpoint a particular parameter that would reliably separate “remodellers” from “non-remodellers,” and the definitions of remodelling itself, based on left ventricular volumes, are somewhat arbitrary. Nevertheless, some patients progress inexorably to terminal heart failure, while in others the response to the initial ischemic injury seems to come to a morphologic and functional standstill.

In the past, several factors have been identified as contributors to the process of left ventricular post-infarction remodelling:

- Infarct size: larger infarcts more frequently lead to remodelling (confirmed in the study by López Haldón et al. published in this issue of Revista Española de Cardiología).
- Apical versus other infarct locations: the apex appears to be particularly vulnerable, perhaps due to its thin walls and low curvature radius (confirmed in the study by López Haldón et al.).
- Lack of reperfusion therapy or lack of successful reperfusion at the myocardial tissue level; this has been documented by myocardial contrast echocardiography, originally applied by intracoronary injection and, more recently, by intravenous route. The present study showed a trend towards longer ischemia time in remodellers.
- Development of new mitral regurgitation, which was not confirmed in the present study, but may have been due to relatively early imaging (median, 5 days) after infarction.

The study by López Haldón et al. extends our insight into left ventricular remodelling by using a simple echo parameter, the ratio E/e’ of maximal transmitral E velocity to early diastolic tissue velocity at the base of the left ventricle e’ (we will use this notation, which is recommended...
by guidelines, instead of Em). This ratio has been shown in a number of studies to correlate with left ventricular diastolic pressure, both in patients with preserved as well as reduced left ventricular function. The parameter now plays a central role in the evaluation of diastolic function by echo.\textsuperscript{7,8} In the study by López Haldón et al\textsuperscript{2} of 159 patients after ST elevation infarction treated by apparently successful percutaneous intervention, an elevated E/e’ ≥14 predicted left ventricular remodelling after 6 months, defined as an increase in end-diastolic left ventricular volume of at least 20% compared to baseline, with a sensitivity of 70% and specificity of 68%. The predictive power was superior to classic echo parameters such as baseline left ventricular volumes, ejection fraction, and E wave deceleration time. In a multivariate model, E/e’ was the only independent predictor of remodelling.

From these findings, we may infer that in patients at risk for remodelling, left ventricular diastolic pressures are already elevated shortly after infarction, signalling that the diastolic pressure-volume relation of the left ventricle has changed in response to ischemic injury. Since patients who later showed remodelling did not differ appreciably in ejection fraction from those who didn’t, this indicates that diastolic pressures are an earlier and apparently more sensitive parameter of functional damage of the left ventricle than ejection fraction. Notably, in the cohort of the present study,\textsuperscript{2} only 7.5% had an ejection fraction below 40% at discharge, reflecting relatively well-preserved systolic function in the majority of these patients. It is in these patients that risk stratification may be particularly beneficial, since those with severely impaired function are already likely candidates for remodelling and also for maximal heart failure therapy with drugs and other interventions.

An interesting perspective that these data offer is whether combining E/e’ determination with exercise—the “diastolic stress test”—might further improve the predictive power of echo. The “diastolic stress test”\textsuperscript{9,10} has been shown to unmask diastolic dysfunction which is not clear-cut at rest, and this might be an even better instrument to identify patients on the path to functional deterioration who go unnoticed by looking at systolic function only and have equivocal findings of diastolic function at rest.

The relation of echo parameters of diastolic function to post-infarction prognosis in general (not necessarily mediated by remodelling) has been analyzed earlier. Most prominently, shortened mitral E wave deceleration time and the restrictive mitral inflow pattern\textsuperscript{9,11} was found to predict adverse events independently from ejection fraction. Enlarged left atrial volume has been found as a good predictor of adverse events, but its predictive specificity is limited due to other conditions leading to left atrial enlargement, most prominently, of course, atrial fibrillation. E/e’ has been reported from the Mayo Clinic as the most powerful independent post-infarction predictor of adverse prognosis from a large number of clinical and echocardiographic variables, including ejection fraction and E wave deceleration time.\textsuperscript{12} In the largest study to date,\textsuperscript{13} looking at 400 post-infarction patients, indexed left atrial volume >32 mL/m² was a predictor of adverse outcomes, but with a hazard ratio of 3.35 it was a much weaker predictor than a E/e’ >15 (hazard ratio = 6.14), which was the strongest echo predictor. E wave deceleration <150 ms had a hazard ratio of 3.15, almost identical with left atrial size. This study, like the work of López Haldón et al, also analyzed natriuretic peptide levels and found them similarly predictive as E/e’ for prognosis.

Some other aspects of the study\textsuperscript{2} deserve comment. López Haldón et al used septal e’ only for calculating E/e’, while current guidelines recommend averaging septal and lateral values, since such an average intuitively is more representative of early diastolic relaxation and lengthening of the whole ventricle than a single measurement; further, some validation studies for this parameter have used averaged e’. However, several conditions may lead to large differences in septal and lateral e’ and hence reduce the utility of averaging these values, e.g., left ventricular asynchrony in bundle branch block or pacemaker stimulation, and the fact that measuring lateral e’ in dilated ventricles frequently results in data which reflect both radial and longitudinal velocities of E/e’. The issue is unresolved and perhaps unsolvable if simplicity of use is to be preserved.

The authors excluded from analysis 9 patients who died during the first 6 months, as well as 5 with reinfarction, and 3 with “disease progression with clinical symptoms.” One wonders whether this decision might not have excluded mainly patients prone to remodelling and therefore perhaps diluted the findings of the study.

Is it preferable to simply measure natriuretic peptides and forget about the intricacies of diastolic function to anticipate left ventricular remodelling? The present work,\textsuperscript{2} confirming an earlier report,\textsuperscript{14} indicates that the answer is no. Although truly low NT-proBNP values reliably exclude increased diastolic pressures and heart failure, no firm, “recommendation-grade” evidence for other uses of this parameter in the post-infarct or heart failure scenario has emerged.
In particular the value of changes in NT-proBNP levels to guide therapy is controversial.\textsuperscript{15,16} For the time being, echocardiography—which is uniformly recommended by current guidelines in post-infarction patients—offers far better clinical guidance in these patients; with the downside that it is also far more complex than a single number and must be interpreted correctly.

The present work\textsuperscript{2} advances our understanding of left ventricular post-infarction remodelling and suggests that $E/e'$ is a useful parameter to measure (certainly at rest, but perhaps in some cases also during an exercise test) to identify left ventricular remodelling with its attendant elevated risk of adverse events. Such patients might benefit from more vigorous medical therapy targeted to decrease diastolic pressures even in the absence of an impairment of pump function and hence in the absence of a classic indication for heart failure therapy. Whether such a strategy in the end can reduce mortality and morbidity, however, must be studied in the future.

REFERENCES

Flachskampf FA et al. Raised Diastolic Pressure After Infarction

echocardiography, and B-type natriuretic peptide. Am Heart J. 2010;159:47-54.