LETTERS TO THE EDITOR

Expression of Angiotensin II Receptors in Human Left and Right Atrial Tissue in Atrial Fibrillation With and Without Underlying Mitral Valve Disease

Atrial fibrillation (AF) causes various changes in atrial electrophysiology and morphology (1). Recently, an increased activity of the atrial angiotensin II (AngII) system was found in patients with AF and concomitant structural heart disease (SHD) (1–3). This corresponds to an increased amount of atrial fibrous tissue. The initial trigger for activation of the AngII system typically is the underlying ventricular disease and not AF per se (1).

Boldt et al. (4) tried to analyze the expression of AngII receptors type 1 (AT1) and 2 (AT2) in patients with and without mitral valve disease (MVD). The investigators claim that AT1 is upregulated in fibrillating left atria, whereas AT2 remains unchanged. These findings are contrary to results from our group (3).

How can these differences be explained? When dealing with receptor expression in humans, defining "controls" is an important issue. This is especially true when determining the real impact of the arrhythmia on angiotensin II receptor (AT) regulation, because concomitant heart diseases dramatically influence AngII levels. Boldt et al. (4) performed a pooled analysis using 74 left atrial tissue samples from patients with AF; 15 patients served as "matched" controls. Their analysis revealed, however, no difference at all in receptor expression between comparable patient groups with MVD ± chronic AF (cAF). Furthermore, patients with MVD and cAF are not different compared to patients with SHD in sinus rhythm (Fig. 5 in Boldt et al. [4]). The only difference, using an unpooled analysis, was between patients in SR (plus SHD) and patients with lone AF (Fig. 5 in Boldt et al. [4]). What does this mean for the pathophysiology of AF? As multiple studies clearly showed, the pathophysiology of lone AF is not equal to AF in the presence of MVD; neither is paroxysmal AF comparable to cAF (1).

A stunning finding of Boldt et al. (4) is the lack of substantial expression of AT1 in patients with SR (Fig. 2 of Boldt et al. [4]), known to be abundantly expressed by all cardiac cell types. Moreover, AT2 expression appears from that figure to be about 10× compared to AT1. Remarkably, both receptor subtypes have the same protein size (52 kDa). The investigators claim to support their findings by immunohistologic analysis, which locates sites of expression rather than allowing quantification.

A direct comparison between left and right atrial tissue was not performed in a single patient. In sum, it remains unclear whether the described differences in AT expression are solely due to the presence or absence of AF or to the impact of present coronary artery/valve diseases.

What can we learn about receptor expression in AF? Expression patterns are clearly time-dependent and, as observed for other signaling pathways, differences exist between right and left atria. In patients with long-lasting AF (average 47 months in our study) a reversal of AT1/AT2 expression may occur similar to ventricular receptor levels during heart failure, which is also characterized by extensive ventricular fibrosis (5). Sustained increase of peptide hormone levels often down-regulates their receptor (5). Down-regulation of AT1 may indeed follow an initial phase of up-regulation. Thus, our previous results do "fit into the pathophysiology." However, the time course of receptor expression has not yet been analyzed.

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REPLY

Atrial fibrillation (AF) is associated with electrical remodeling in the human atria (1), and angiotensin II (AngII) is involved in the process of atrial electrical remodeling (2). Recently, we analyzed the expression of angiotensin II receptor type 1 (AT1) and 2 (AT2) in the human left atrium and were able to show that AF is associated with an up-regulation of AT1 in the human left atrium (3), but not in the human right atrium. Regarding the expression of AT1 in the right atrium, we could show results similar to Goette et al. (4); however, the results were less pronounced than in the study of Goette et al. This might be caused by different patient populations. Furthermore, we could clearly demonstrate that an underlying mitral valve disease (MVD) did not have any significant influences on the expression of AngII receptor subtypes (Fig. 4A to 4D in Boldt et al. [3]). Other possible effects of an underlying MVD were not mentioned in our study.

Goette et al. (4) claimed a direct comparison between left and right atrial tissue in a single patient. For ethical reasons it was not possible to obtain atrial tissue samples of both atria of a single patient, a fact that concerns most of the other study groups.
However, an animal model would provide results that may help to understand pathophysiological mechanisms in AF.

In our study (3), we did not assert to use the immunological analysis for quantification. After finding clear histological differences (by visualization) between patients in sinus rhythm (SR) and AF, we quantified the expression of AT1 and AT2 by Western blot techniques. We could detect a significant increase in AF compared to SR in the AT2 expression, but not in the AT1 expression (Fig. 3A [3]). As shown in Figure 2, there was a higher level of AT1 in patients with both lone AF and MVD + AF compared to a lower level in patients with SR. In contrast to the claim of Goette et al., there was no lack of expression of AT1 in SR; however, a low level (Fig. 2 [3]).

We cannot exclude that other substrates or pathways may influence the expression of AT1/AT2 in patients with AF. However, a time-dependent expression of AT1 has not yet been analyzed and is difficult to investigate in humans. In fact, differences exist in the expression of angiotensin II receptor subtypes between human left and right atrium. Furthermore, because AF depends from the left atrium (5), it is important to consider both atria to draw possible conclusions about pathophysiological influences of signaling pathways. Owing to our results, AF is associated with an upregulation of AT1 in the left atrium, but not in the right atrium. This suggests a pathophysiological role of AT1 in AF (3,6,7).

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From Controlled Trials to Clinical Practice: Monitoring Transmyocardial Revascularization Use and Outcomes

Considering the significant clinical experience with transmyocardial revascularization (TMR) in both the controlled trial and “real-world” setting, we felt compelled to comment on the recent retrospective registry report by Peterson et al. (1) culled from the Society of Thoracic Surgeons national cardiac database. Regarding sole-therapy TMR, the investigators confirm findings observed in five prospective randomized trials comparing TMR to medical therapy in “no option” class III/IV angina patients: like most new technologies, there is a learning curve, and surgical risk is increased in sicker patients (2–6). Their commentary, similarly, is not new. Allen et al. (2) reported reduced operative mortality rate from 5% overall to 2% in the last 100 randomized patients, attributable to surgical technique refinement and patient selection; Frazier et al. (3) reported unstable angina as a significant predictor of operative mortality. Others with clinical experience in treating unstable patients (2,7,8) confirmed that such patients without conventional options represent a higher risk group for TMR.

Although not the intent of their retrospective study, Peterson et al. (1) fail to summarize adequately the clinical benefits of sole-therapy TMR. In prospective randomized trials at one year, TMR provided superior angina relief, decreased rehospitalizations, and improved exercise times compared to patients managed medically. A recent five-year follow-up of randomized patients demonstrated significantly increased Kaplan-Meier survival rates and sustained, significantly superior angina relief in patients randomized to TMR compared to medical therapy (9).

As reported by the investigators (1), TMR is increasingly being utilized adjunctively with coronary artery bypass grafting (CABG) in patients with diffuse coronary artery disease (CAD) who would be incompletely revascularized by CABG alone. In a prospective, randomized trial involving 263 such patients, CABG/TMR provided operative and one-year mortality benefits with a trend toward superior angina relief compared to CABG alone (10). The retrospective report by Peterson et al. (1) compares patients in the STS database who received CABG/TMR with a matched control group consisting of CABG-only patients with triple-vessel disease who received <3 grafts. The appropriateness of this comparison is questionable, because it assumes that incomplete revascularization in the control group occurred in an area of ischemic viable myocardium supplied by a diffusely diseased, ungradable coronary artery and that all participating centers accurately and consistently defined three-vessel disease. It is not possible to verify this by simply querying the STS database. It is important also to note that surgeons are increasingly operating on patients with diffuse-CAD, which has been shown to be a powerful independent predictor of operative mortality (11,12). Unfortunately, the presence of diffuse-CAD is not factored into the STS database or other national databases. Thus, such case-matched comparisons against CABG/TMR-treated patients with diffuse-CAD can be unreliable because control database sources fail to account for diffuse-CAD and therefore underestimate predicted operative mortality in this select patient group.

We applaud the investigators in supporting continued physician training and education regarding the judicious application of sole-therapy TMR or adjunctively in patients who would be incompletely revascularized by CABG alone. Long-term