Reviewer's report

Title: ACE-inhibition attenuates uremia-induced aortic valve thickening in a novel mouse model

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Reviewer: Robert Weiss

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'ACE-inhibition attenuates uremia-induced aortic valve thickening in a novel mouse model' Mikko A Simolin et al.

This report by Simolin et al addresses an important problem in cardiovascular medicine: the link between kidney disease and cardiovascular disease. The main findings are that moderate uremia is associated with aortic valve leaflet thickening, and that treatment with an angiotensin converting enzyme inhibitor results in thinner aortic valve leaflets than no treatment.

Major Compulsory Revisions

1. There appears to be a major influence of aging upon the thickness of aortic valve leaflets. Mice in the 0 NX group, those with presumably normal renal function, undergo an increase in leaflet thickness of about 80% between age 22 weeks and 36 weeks. This effect is greater than the change caused by uremia, which appears to increase leaflet thickness by about 25 – 35%. Thus, the effect of 5/6 NX does not achieve statistical significance when compared to 0NX, at age 36 weeks. Unfortunately, no mice in the 0 NX group received enalapril treatment. Thus, we cannot be sure that the effect of enalapril, which decreased leaflet thickness, was specific for uremia-related valve growth as opposed to the normal growth of aging. The authors should provide more data or a convincing rationale to substantiate the specificity of the enalapril effect on uremia-related pathology.

2. In this setting, it is not even clear that the increase in valve thickness is deleterious, since substantial thickening occurs with age alone. The authors could address this question by description of the tissue composition in uremic valves. Is it mainly cellular hyperplasia or hypertrophy? Are there inflammatory cells present, more so in uremic valves? What is the apparent lipid content? Collagen? Calcium? Whereas strict quantitation of these moieties might be beyond the scope of the present investigation, systematic qualitative comment would strengthen the study.

3. The potential mechanisms of action of enalapril warrant further discussion. The authors speculate that plasma renin levels were probably decreased in the uremic mice – a difference from many clinical states (diabetes, renovascular disease, hypertension), which tend to be high-renin conditions. Nevertheless, the authors note, correctly, that most ACE resides in the lung, and there are important levels of ACE in valve tissue. A key question is whether ACE levels are
upregulated in uremia. The Methods section, p. 6, mentions “ACE-activity” assays, but I do not find them in the tables or figures. Are they increased by NX? Does enalapril treatment lower them?

4. Classically, renin synthesis is the rate-limiting step in formation of angiotensin II. If the NX model causes low renin, then how would ACE inhibition be beneficial specifically in this model, as opposed to a non-specific effect on valve tissue? Is there a bradykinin effect?

5. In the 36 week model, enalapril treatment appears to be associated with lower systolic blood pressure and lower cholesterol. Can those non-specific effects be excluded as principal mediators of the drug’s effect on valve tissue? Statistical comparisons among individuals within each group might be enlightening.

Minor Essential Revisions

1. Table I reports mean blood pressure = 116, whereas Table II reports systolic blood pressure = 112. Is one of these in error? The same convention should be employed in both tables.

2. Methods description should be slightly more detailed. For example, if blood pressures were measured using the tail cuff method, it should be explicitly stated. A brief description of the definition of “plaque area” would be helpful.

3. In Figure 2, panel B and C, there appears to be a significant amount of “aortic plaque”, if that definition includes intimal hyperplasia. However, the data in Tables I and II indicate that plaque areas all less than 1%. Is that correct?

Discretionary Revision

In O NX mice, the plasma creatinine levels are about 5-fold higher in the present study than in previous reports, and in fact are similar to creatinine levels previously reported in NX mice (refs. 21 and 22). An explanatory comment would be helpful.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.