

and alterations in autonomic tone that occur after cardiac surgery and resolve over time.<sup>4,5</sup>

The relatively high rate of stroke or TIA in the present study (1.1% over a 60-day period of follow-up) leads me to wonder whether a lower threshold for anticoagulation may be appropriate to attempt to lower the stroke rate. Thus, I would encourage this study group to design a new trial to address the most effective approaches to anticoagulation in patients with postoperative atrial fibrillation. It appears that the indication for the initiation of anticoagulation after cardiac surgery in this study (atrial fibrillation for >48 hours) differs considerably from the indication in patients with atrial fibrillation in the nonsurgical setting.<sup>2</sup>

The present study evaluating the effectiveness and safety of rate control versus rhythm control for new-onset atrial fibrillation or atrial flutter after cardiac surgery supports the null hypothesis. Although the authors conclude that either strategy is reasonable after cardiac surgery, I would interpret the study results differently. It seems that the findings support the concept that the initial goal should be rate control because no clear benefit of the more complex rhythm-control strategy was observed. Efforts to restore sinus rhythm should be reserved for patients in whom rate control cannot be achieved or for those who are hemodynamically unstable or highly symptomatic. The all-too-frequent knee-jerk reaction to perform cardioversion in patients with postoperative atrial fibrillation with hopes of reducing the risk of stroke, the need for anticoagula-

tion, and the duration of hospitalization seems hard to justify, given the well-known risks and costs associated with such interventions and the absence of clear beneficial effects of the rhythm-control strategy. I believe that this large landmark study, which showed that rate control and rhythm control result in equivalent outcomes for patients with postoperative atrial fibrillation, will have an immediate effect on the care of patients, since it will shift the balance of strategies toward rate control.

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## Telomeres on Steroids — Turning Back the Mitotic Clock?

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In a study reported in this issue of the *Journal*, Townsley et al. found that patients with diseases that are thought to result from defective telomere maintenance benefit from treatment with androgenic anabolic steroids.<sup>1</sup> All 12 of the patients they examined had normalization of their leukocyte telomere attrition rate,<sup>2</sup> and 11 of the 12 had evidence of telomere elongation instead of telomere loss. These are exciting findings that

provide food for thought about the role of telomeres and telomerase in hematopoietic stem cells.

The role of telomerase in hematopoietic stem cells has been puzzling ever since the first reports of the loss of telomeric DNA with age in both human leukocytes<sup>3</sup> and purified hematopoietic stem cells.<sup>4</sup> Does telomere attrition serve to suppress clonal proliferation of abnormal stem

cell clones? Observations that support this notion have to be contrasted with data showing that critically short telomeres may drive tumor progression in chronic myeloid leukemia<sup>5</sup> and other cancers. Does variable telomerase expression in different cell types explain why loss of p53 and aneuploidy are much more common in carcinomas than in hematologic cancers or why B-cell lymphomas are much more common than T-cell lymphomas? What is the role of telomerase in hematopoietic stem cells?

The telomere length in all leukocytes except memory B cells<sup>6</sup> declines considerably during the first few years of life<sup>7</sup>; this decline is in line with the concept of a telomere-based “mitotic clock” in hematopoietic stem cells that ticks with every cell division. Yet telomerase activity is readily detectable in purified hematopoietic stem cells.<sup>8</sup> The role of telomerase in human hematopoietic stem cells has become more clear as a result of pioneering studies involving patients with dyskeratosis congenita.<sup>9</sup> Studies of this heritable disease have found that a moderate reduction in telomerase levels — resulting from haploinsufficiency for either *TERC*, the telomerase RNA template gene, or *TERT*, the telomerase reverse-transcriptase gene — can give rise to a clinically diverse spectrum of “telomere maintenance” disorders. On the basis of these studies, it appears that telomerase levels in hematopoietic stem cells are insufficient to prevent overall telomere loss but are nevertheless crucial for the prevention of stem-cell exhaustion. One possibility is that “wild-type” levels of telomerase are needed to repair sporadic damage to telomeric DNA. Such telomerase-mediated repair of telomeres could be compromised in the “telomere maintenance” disorders, with bone marrow failure occurring as a result. Perhaps hematopoietic stem cells undergo apoptosis in response to sustained DNA damage signals originating from critically short, unrepaired telomeres. Extra cell divisions in remaining hematopoietic stem cells, with the same telomere repair defect, could initially result in the very short telomeres typically seen in these disorders and eventually in stem-cell exhaustion and bone marrow failure. Of note, whereas aplastic anemia is clinically the most serious phenotype in younger patients, the most common clinical manifestation in patients older than 30 years of age is pulmonary fibrosis.<sup>10</sup>

Whether this reflects defective telomere repair in lung epithelial cells, T cells, or natural killer cells or in a combination of these cells resulting in failure to clear senescent lung cells is currently not known.

The findings of Townsley et al.<sup>1</sup> support the idea that an elevation in telomerase levels through treatment with androgens results in modest leukocyte telomere elongation (instead of the expected shortening) in patients with disorders characterized by very short telomeres, as well as the idea that such telomere elongation is associated with improvements in blood counts. The observed gains in telomere length were, on average, 360 bp after 1 year, with marked variation among patients. Telomere lengths were measured with the use of two independent methods and, when these data are combined with those from previous studies cited in the article, they leave little doubt that significant and clinically relevant telomere elongation can be achieved through treatment with androgens in these patients. Previous studies by the same group indicate that this activity is most likely mediated through the estrogen-responsive element in the promoter of the *TERT* gene.<sup>11</sup>

Elongation of telomeres through androgen treatment may have applications in the treatment or prevention of other diseases linked to defective telomere maintenance. Specifically, the effect of this treatment on lung and liver in older patients with these disorders needs to be examined. Further studies are also needed to establish the dose and duration of treatment. Because significant effects on telomere length were already observed after 6 months, this time point could possibly be used to evaluate effectiveness in future studies.

Telomere elongation with the use of androgens or other compounds may help prevent “telomere crisis” in association with those disorders in which the biggest risk to the patient is malignant progression of the disease through telomere-mediated genome instability. For all these possible clinical interventions, more information about the role of telomerase and telomeres in the biology of various normal, premalignant, and malignant cells is urgently needed.

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