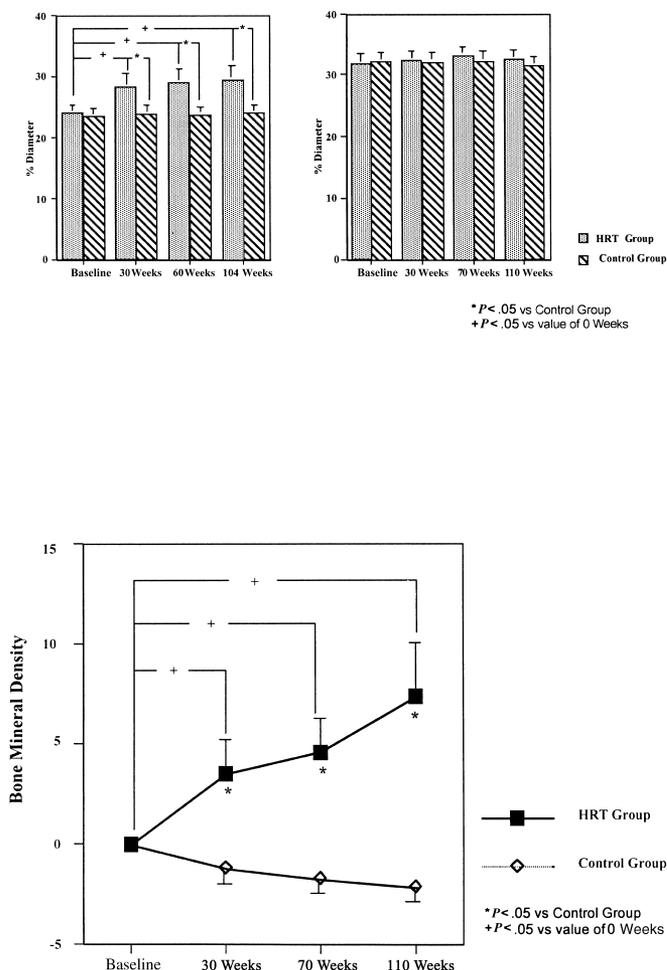


## THE LONG-TERM EFFECT OF ESTRIOL ON ENDOTHELIAL FUNCTION AND BONE MINERAL DENSITY IN OCTOGENARIAN WOMEN

*To the Editor:* Hormone replacement therapy (HRT) decreases coronary events in postmenopausal women. However, the Heart and Estrogen Replacement Study showed that such therapy carries a risk of thrombotic complications.<sup>1</sup> The effects of HRT in older women are thus controversial. The direct action of estradiol on the vessel wall has been studied vigorously in this decade. In our previous study, we demonstrated that estradiol retards the progression of severe atherosclerosis in rabbits.<sup>2</sup> More than 50% of its antiatherosclerotic effects were subsequently suggested to be due to this direct action.<sup>3</sup> HRT is believed to be ineffective for osteoporosis in older people because of the low bone turnover in such patients. In this study, we investigated the vascular and bone effects of estrogen on octogenarian females. We selected estriol (E3), which shows a degree of extragenital effects comparable with that of 17- $\beta$  estradiol (E2) but weak genital influence.<sup>4</sup> We investigated 24 older women (mean age  $\pm$  standard deviation: 80.3  $\pm$  3.5) who were administered 1 g/day CaC<sub>12</sub> with (HRT group; n = 12) or without (control group; n = 12) 2 mg/day E3 (Mochida Pharmaceutical Co., Tokyo, Japan) for 110 weeks. Their bone mineral densities (BMDs) were  $-3.5 \pm 0.3$  of average BMD. They were in geriatric nursing homes but were active and had no history of ischemic cardiovascular diseases. All patients provided informed consent. Vascular function was evaluated as described previously.<sup>5</sup> In brief, the changes in diameter of the right brachial artery were measured during reactive hyperemia as percentage flow-mediated dilatation (%FMD) and after sublingual nitroglycerin spray (300  $\mu$ g), which causes endothelium-independent vasodilatation (percentage nitroglycerin-induced dilatation (%NTG-D)). Blood sampling was performed at 0, 8, 30, 70, and 110 weeks after treatment. Two unpaired Student's *t* tests and Pearson's correlation coefficient were performed. Serum concentrations of total cholesterol; triglyceride; and apoproteins B100, C2, and E were unchanged in all patients. In contrast, levels of high-density lipoprotein cholesterol and apoprotein A1 were significantly increased after 70 weeks of treatment. The values of plasma E3, 17 $\beta$ -E2, and estrone (E1) at 0, 8, and 110 weeks (in pg/ml) were as follows: for E3, less than 5, 43.6  $\pm$  7.2, and 41.4  $\pm$  8.1, respectively ( $P < .01$  vs the value at 0 weeks); for E2, 4.6  $\pm$  0.8, 30.8  $\pm$  8.1, and 16.2  $\pm$  3.8, respectively ( $P < .01$  vs the value at 0 weeks); and for E1, less than 5, 10.8  $\pm$  4.9, and 7.8  $\pm$  3.9, respectively ( $P < .05$  vs the value at 0 weeks). All these levels were unchanged in the control group. The %FMD in the HRT group was increased during the 110 weeks (Figure 1). No difference in %NTG-D was demonstrated between the two groups (Figure 1). Plasma nitrite/nitrate (NO<sub>2</sub><sup>-</sup>/NO<sub>3</sub><sup>-</sup>) and cyclic guanosine 3'5' monophosphate (cGMP) levels also were increased by HRT (data not shown). BMD was estimated by a digital image processing and x-ray film of right hand bone mass, which showed a significant linear correlation with BMD measured by dual energy x-ray absorptiometry in vertebrae ( $r = 0.796$ ).<sup>6</sup> BMD was increased by HRT but was slightly decreased in the control group (Figure 1). Bone formation was assessed by serum



**Figure 1.** Upper left: Endothelial function assessed by measuring dilatation of brachial artery using high-resolution external vascular ultrasound in response to reactive hyperemia (flow-mediated dilatation). Mean percentage increase  $\pm$  standard deviation in vessel diameter is shown. Upper right: Endothelial independent function assessed by measuring dilatation of artery in response to sublingual nitroglycerin infusion. Percentage increase is shown. No significant differences were observed. Lower: Mean  $\pm$  standard deviation changes in bone mineral density from baseline to week 110, expressed as mean percentage change. \* $P < .05$  vs control group,  $^{\dagger}P < .05$  vs value of 0 weeks.

osteocalcin and by carboxyl terminal propeptide of type I procollagen and was shown to decrease more in the HRT group (data not shown). Bone resorption, as assessed by urinary excretion of pyridinoline cross-linked peptides and tartrate-resistant acid phosphatase, slightly increased in the control group but decreased in the HRT group, and the difference between groups was significant (data not shown). No abnormal data were noted in the other biochemical measurements. No adverse effects were observed except for genital bleeding in two treated cases. This is the first clinical report of an as-much-as-2-year-long, E3-induced improvement in endothelial function and bone metabolism in octogenarian women. The effect of HRT in older women for primary prevention of coronary disease was not determined. Because nitric oxide (NO) has many antiathero-

sclerotic effects, improvement of NO-related responses to estrogen may partially explain its antiatherosclerotic effects, which was supported by the increase in  $\text{NO}_2^-/\text{NO}_3^-$  and cGMP observed here. FMD constitutes NO function, and its impairment was reported to precede coronary artery disease.<sup>7</sup> In the octogenarian women studied here, bone turnover was not slow, which is consistent with the results of recent papers.<sup>8,9</sup> In this work, E3 treatment improved BMD. E3 was well tolerated throughout the study. Their high plasma E3 (80 and 76 pg/ml) and E2 (53 and 81 pg/ml) concentrations, which were the highest among all patients, may have caused the genital bleeding observed in two patients. Although our data could not distinguish which hormone (E3 or E2) was responsible for the results in this study, it seems likely that E3 was responsible. Because E3 produces little mitogenic activity, it is less likely to cause side effects such as endometrial cancer. In addition, E3 binds with the same receptors as E2 and can thereby act to protect the reproductive organs.<sup>10</sup> Unlike E2, E3 does not affect the plasma coagulation factors or plasminogen levels.<sup>11</sup> Because estrogen upregulates NO synthase in human osteoblast-like cells, E3 may improve osteoporosis as a bone formation factor and by inhibiting bone resorption.<sup>12</sup> However, the possibility of E2 exerting such effects is slight, because its concentration decreased after 70 weeks. We assume the interference of a transient increase of plasma E2 concentration in response to occupation of common receptors by E3. In conclusion, in the present study, E3 increased BMD and improved endothelial function without significant adverse effects in octogenarian women with osteoporosis.

Toshio Hayashi, MD, PhD  
Hatsuyo Kano, MD  
Daigo Sumi, MS  
Akihisa Iguchi, MD, PhD  
Department of Geriatrics  
Nagoya University Graduate School of Medicine  
Nagoya, Japan

Izumi Ito, MD, PhD  
Hidetoshi Endo, MD, PhD  
Department of Internal Medicine  
National Chubu Hospital  
Oobu, Japan

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## IMPROVEMENT OF COGNITIVE FUNCTION AFTER PACEMAKER IMPLANTATION IN VERY OLD PERSONS WITH BRADYCARDIA

*To the Editor:* Bradyarrhythmias, both sick syndrome and complete atrioventricular block, frequently occur in older people. The main clinical symptoms are syncope, presyncope, and dizziness.<sup>1</sup> It has been also suggested that patients suffering from very slow heart rate may show intellectual decline<sup>2–8</sup> and that the treatment with an artificial pacemaker may improve their cognitive functioning. However, the studies are not all in accordance, included only small numbers of patients,<sup>4,7</sup> were not controlled,<sup>7</sup> or had a very short follow-up,<sup>6,7</sup> so that the question remains unanswered.

We performed a study to assess cognitive performance of consecutive old patients undergoing permanent pacemaker primoimplantation for permanent or paroxysmal bradycardia and, for comparison, in old patients undergoing replacement of permanent pacemaker.

Inclusion criteria were age 65 and older, need for permanent pacemaker implantation because of permanent or paroxysmal bradycardia, and consent to participate. Exclusion criterion was implantation after myocardial infarction or cardiac arrest. The control subjects were recruited from the same department of cardiac pacing after giving informed consent. The diagnosis of dementia was made according to Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition).<sup>9</sup>

Cognitive assessments were made before pacemaker implantation, then at 5 days and 6 months later. The same investigator conducted all assessments (CB). This evaluation included Folstein's Mini-Mental State Examination (MMSE); the paired word-learning test from the Wechsler memory scale; a word fluency test with two categories of words, animals, and fruits; and cube drawing.<sup>10,11</sup> The assessment also included the Geriatric Depression Scale,<sup>12</sup> and the Katz assessment of activities of daily living.<sup>13</sup>

During the period of the study, of 32 eligible patients, two declined to participate and four could not be assessed before implantation; 26 patients participated in the study, and 15 patients served as controls.

Patients and controls were not different with regard to age (mean  $\pm$  standard deviation:  $75 \pm 6$  vs  $76 \pm 6$ ), gender, medications, cardiac diseases, or main associated disorders. Mean heart rate (beats per minute) was significantly lower ( $P$  MA2C .05) in the patient group ( $54 \pm 18$ ; range 20–89) than in the control group ( $64 \pm 7$ , range 50–80). Patients were implanted because of atrioventricular block ( $n = 12$ ), sick sinus syndrome ( $n = 14$ ), or chronic atrial fibrillation ( $n = 2$ ).