Effects of Music Therapy on Autonomic Nervous System Activity, Incidence of Heart Failure Events, and Plasma Cytokine and Catecholamine Levels in Elderly Patients With Cerebrovascular Disease and Dementia

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SUMMARY

Music therapy (MT) has been used in geriatric nursing hospitals, but there has been no extensive research into whether it actually has beneficial effects on elderly patients with cerebrovascular disease (CVD) and dementia. We investigated the effects of MT on the autonomic nervous system and plasma cytokine and catecholamine levels in elderly patients with CVD and dementia, since these are related to aging and chronic geriatric disease. We also investigated the effects of MT on congestive heart failure (CHF) events.

Eighty-seven patients with pre-existing CVD were enrolled in the study. We assigned patients into an MT group (n = 55) and non-MT group (n = 32). The MT group received MT at least once per week for 45 minutes over 10 times. Cardiac autonomic activity was assessed by heart rate variability (HRV). We measured plasma cytokine and catecholamine levels in both the MT group and non-MT group. We compared the incidence of CHF events between these two groups. In the MT group, rMSSD, pNN50, and HF were significantly increased by MT, whereas LF/HF was slightly decreased. In the non-MT group, there were no significant changes in any HRV parameters. Among cytokines, plasma interleukin-6 (IL-6) in the MT group was significantly lower than those in the non-MT group. Plasma adrenaline and noradrenaline levels were significantly lower in the MT group than in the non-MT group. CHF events were less frequent in the MT group than in the non-MT group ($P < 0.05$). These findings suggest that MT enhanced parasympathetic activities and decreased CHF by reducing plasma cytokine and catecholamine levels. (Int Heart J 2009; 50: 95-110)

Key words: Music therapy, Cardiac autonomic activity, Heart rate variability, Cytokines, Catecholamine, Heart failure

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THE elderly population in Japan is increasing rapidly, and people older than 65 will compose approximately 25% of the entire population in 2025.[1] Therefore, containing costs related to the health insurance system for senior citizens older than 75 poses challenges to the national budget of the Japanese Government. As a result of this aging of the population, the prevalences of cerebrovascular disease (CVD) including cerebrovascular infarction and Alzheimer's disease are increasing, and this tends to be followed by a deterioration of activities of daily living (ADL), especially among the elderly who live in residential facilities.[2,3] Currently, in such facilities, the presence of agitation and confusion in the elderly is considered one of the foremost management problems because it interferes with quality of life.[4,5]

Confused and agitated patients are currently managed using medications and physical restraint. However, these particular interventions may create additional physiological effects beyond those of the original agitation.[6] Therefore, alternative approaches that reduce the need for psychotropic medications or physical restraint in the treatment of elderly people are required, especially for those with dementia. One such approach is the use of music, which promotes relaxation in the community and is widely applied in some residential facilities for the elderly, hospitals, and hospices to induce a calming, positive ambience.[7-10] Music is used to reduce psychological stress in several fields of medicine, including cardiovascular care -- it is widely used during percutaneous coronary intervention (PCI) and in the cardiac care unit (CCU).[11-14] However, it has not yet been clearly demonstrated to reduce the incidence of disease, and its pathophysiological action on the autonomic nervous system remains to be clarified. In the present study, we therefore studied the effects of music on the relaxation response, focusing on autonomic nervous system activity, heart failure events, and plasma cytokine levels. We chose to investigate these variables because the literature contains much research on the relationship between psychological stress and cardiovascular disease[15,16] and plasma levels of cytokines such as interleukin 6 (IL-6) and tumor necrosis factor (TNF) that are reportedly related to aging and chronic geriatric disease.[17-21] We also measured levels of plasma catecholamines, as these down-regulate cytokines such as IL-6, and this down-regulation is thought to be influenced by both aging and autonomic nervous activity.[18]

Methods

Patients: The present study enrolled 87 patients (aged 82.3 ± 9.6 years) with advanced dementia who had been admitted to our hospital with pre-existing CVD. The presence of CVD was diagnosed from brain CT at the time of admission. We assigned the patients to a music therapy (MT) group (n = 55, age; 84

± 9 years) or a non-MT group (n = 32, age; 81 ± 7 years) on a nonrandomized basis. The MT group received MT once per week at least 10 times continuously (described below), whereas patients in the non-MT group did not receive MT. To avoid possible confounding effects, patients were excluded if they had a concomitant condition known to have an independent effect on autonomic activity such as clinical evidence of autonomic neuropathy or any acute inflammatory disease, acute coronary ischemia, other acute illness, or malignancy. The study was conducted during the course of routine care in accordance with the principles of the Helsinki Declaration,[22] and informed consent was obtained mainly from family members. All subjects underwent a standard clinical evaluation including medical history, neurological examination, cognitive function assessment, chest X-ray, ECG, and brain CT. Diagnosis of dementia was made by consensus at a conference of physicians, nurses, and care workers on admission and was based on results of the Mini-Mental State Examination.[23] We compared clinicodemographic characteristics such as age, gender, level of dementia, CT findings, pre-existing illnesses (e.g., CVD, diabetes mellitus (DM), and congestive heart failure (CHF)), and medication use between the two groups. We also compared the incidences of acute heart failure and exacerbation of CHF during the period of hospitalization between the two groups. Patients were defined as having CHF if they had relevant signs and symptoms for at least one week classified as at least NYHA stage 3 or above, based on ACC/AHA guidelines,[24] and/or signs of pulmonary edema on chest X-ray, and/or a cardiothoracic ratio > 0.55. Death due to CHF was defined as that occurring after a documented period of symptomatic deterioration of heart failure. The mean duration of hospitalization was at least one year in both groups.

Music therapy (MT): MT was performed once per week for 45 minutes from 11.00 to 11.45 am by two experienced and licensed music therapists according to the guideline of the Japanese MT Society. The MT consisted of well-known Japanese nursery rhymes, folk songs, hymns, and recent Japanese popular music.

Heart rate variability (HRV): HRV was obtained using an ambulatory Holter ECG system and two-channel (Fukuda Denshi FMD-150) ECG recorder. Spectral power results were obtained from the first 2-minute segment with a total spectrum of 128 points and frequency ranging from 0.01 to 1.0 Hz. For frequency domain analysis, the low-frequency (LF) band (0.04 to 0.15 Hz), high-frequency (HF) band (0.15 to 0.40 Hz), and power values were calculated using GMS Chiram software.[25] The LF and HF components were expressed as power and were measured as ms^2. The HF component mainly reflects parasympathetic activity, whereas the LF:HF ratio mainly reflects sympathetic activity and sympatho-vagal balance.[26] For time domain analysis, we used the percentage of successive RR-interval differences ≥ 50 ms (pNN50) and square root of the mean of the squared differences between adjacent intervals (rMSSD).[26] These parameters were calculated by the software used for frequency domain analysis and used to express parasympathetic activity.[25,26] HRV was measured before MT (10:00 to 11:00), during MT (11:00 to 11:45), and after MT (14:00 to 15:00). The non-MT group underwent HRV measurements at the same time as the MT group, using the same Holter ECG system.

Laboratory investigations: Blood samples were taken in the morning in the fasting state and all plasma was stored at -70°C in a single batch until subsequent analysis. For the MT group, blood samples were taken within 24 hours after MT. Plasma cytokines (IL-6 and TNF) were measured by ELISA and catecholamine (adrenaline and noradrenaline) levels were measured by HPLA. The intra-assay coefficient of variance was < 5% for all assays.

Statistical analysis: All parameters are presented as the mean ± SD and were analyzed by repeated measures ANOVA. Comparison between the MT and non-MT groups was performed using unpaired *t* tests and two-way analysis of variance with repeated measurements. A *P* value of < 0.05 was considered to indicate statistical significance.

Results

The characteristics of the participants are summarized in Table I. There

Table I. Clinicodemographic Characteristics of Subjects

	MT group (*n* = 55)	non MT group (*n* = 32)	*P*
Age (years)	84 ± 9	81 ± 7	NS
Sex (male/female)	20/35	12/20	NS
Cerebral vascular disease			
Cerebral infarction			
Lacuna infarction	26	13	NS
Non-lacuna infarction	22	13	NS
Cerebral hemorrhage	1	5	NS
Chronic subdural hematoma	1	0	NS
Subarachnoid hemorrhage	3	1	NS
Head injury	2	0	NS
Complication			NS
Diabetes mellitus	6	8	NS
Hypertension	19	10	NS
Chronic heart failure	7	6	NS
Medication			
Ca channel blocker	10	5	NS
β-blocker	4	0	NS
α-blocker	1	5	NS
Minor tranquilizer	16	7	NS

Mean ± SD

Table II. Results of HRV (MT group)

	10:00-11:00	11:00-11:45	14:00-15:00
Mean RR (ms)	784 ± 119	802 ± 224	803 ± 103
rMSSD (ms)	17.4 ± 7.2	24.1 ± 15.5*	19.0 ± 8.7$
PNN50 (%)	2.1 ± 2.8	6.4 ± 10.7*	3.1 ± 4.5$
HF (ms^2)	49 ± 36	108 ± 157*	68 ± 72
LF/HF	3.0 ± 2.9	2.4 ± 2.0	2.3 ± 1.5

*$P < 0.05$ versus 10:00-11:00
$ $P < 0.05$ versus 11:00-11:45

Table III. Results of HRV (non-MT group)

	10:00-11:00	11:00-11:45	14:00-15:00
Mean RR (ms)	799 ± 110	760 ± 102	750 ± 167
rMSSD (ms)	17.6 ± 6.7	18.4 ± 6.1	16.7 ± 5.5
PNN50 (%)	1.6 ± 2.1	1.9 ± 2.0	1.5 ± 1.9
HF (ms^2)	59 ± 59	60 ± 51	43 ± 37
LF/HF	2.8 ± 1.5	3.8 ± 2.3	3.0 ± 2.2

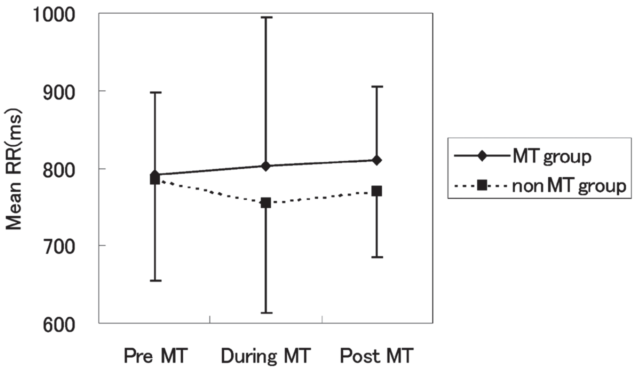

Figure 1. Changes in mean RR. The mean RR did not change significantly in either the MT group or non-MT group.

were no significant differences in age, gender, CVD manifestations, history of DM, hypertension, or CHF, or medication use between the two groups. The MT group received MT an average of 12 ± 2.8 times. Table II shows the HRV parameters in the MT group before, during, and after MT. All parameters except the LH: HF power ratio increased by 10% to 190% immediately after MT and then decreased almost to pre-MT levels. Among the HRV parameters, rMSSD, pNN50, and HF power increased by 40 to 190% ($P < 0.05$) after MT, whereas the LH: HF power ratio decreased by 20% after MT (NS). Table III shows the HRV parameters in the non-MT group. Although the LH: HF power ratio increased by 24 to 35% (NS), other parameters of parasympathetic activity remained relatively stable. The changes in LF power and LH: HF power ratio around noon in the non-MT group might be accounted for by the proximity to lunch time and psychological effects associated with this. However, these changes were not significant. Changes in the HRV parameters are also shown in Figures 1 to 5.

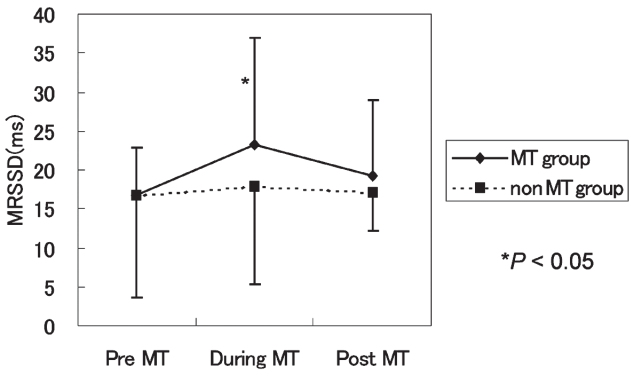

Figure 2. Changes in rMSSD. RMSSD in the MT group increased significantly from 17.4 ± 7.2 ms to 24.1 ± 15.5 (P < 0.05) during MT and decreased to 19.0 ± 8.7 after MT. There was no significant change in rMSSD over a similar time period in patients who did not receive MT.

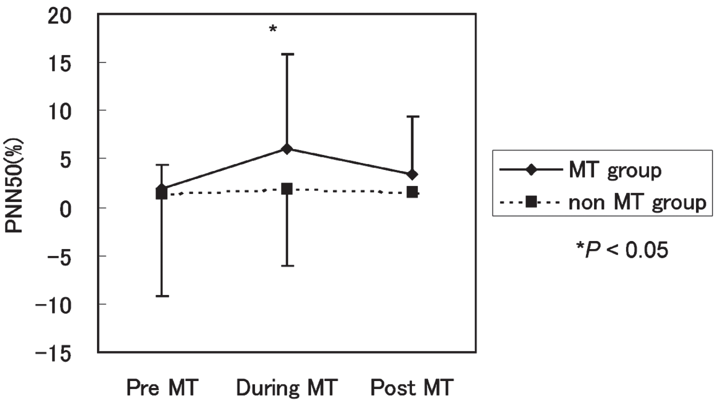

Figure 3. Changes in pNN50. PNN50 in the MT group increased significantly from 2.1 ± 2.8% to 6.4 ± 10.7 (P < 0.05) during MT and decreased to 3.1 ± 4.5 after MT. There was no significant change in pNN50 over a similar time period in patients who did not receive MT. * P < 0.05

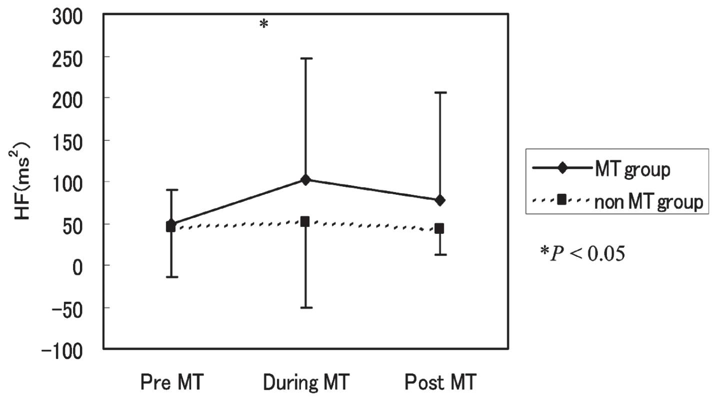

Figure 4. Changes in HF. HF in the MT group increased significantly from 49 ± 36 ms^2 to 108 ± 157 ($P < 0.05$) during MT and decreased to 68 ± 72 after MT. There was no significant change in HF over a similar time period in patients who did not receive MT. * $P < 0.05$

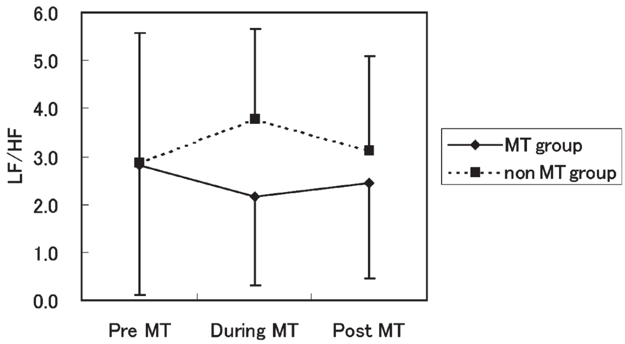

Figure 5. Changes in LF: HF ratio. The LF: HF ratio in the MT group decreased from 3.0 ± 2.9 to 2.4 ± 2.0 during MT and decreased further to 2.3 ± 1.5 after MT. There was no significant change in the LF:HF ratio over a similar time period in patients who did not receive MT.

Figure 6 shows the plasma levels of the proinflammatory cytokines IL-6 (left) and TNF (right). Although plasma TNF levels did not differ significantly between the MT and non-MT groups (8.99 ± 13.7 ng/mL versus 8.04 ± 12.46, NS), the IL-6 level in the MT group was significantly lower than in the non-MT group (7.38 ± 9.03 ng/mL versus 17.29 ± 14.90, $P < 0.05$). Figure 7 shows plasma adrenaline (A) and noradrenaline (B) levels. Similarly, plasma adrenaline and noradrenaline levels in the MT group were significantly lower than those in the non-MT group (adrenaline: 15.33 ± 11.81 pg/mL versus 38.08 ± 20.03, *P* <

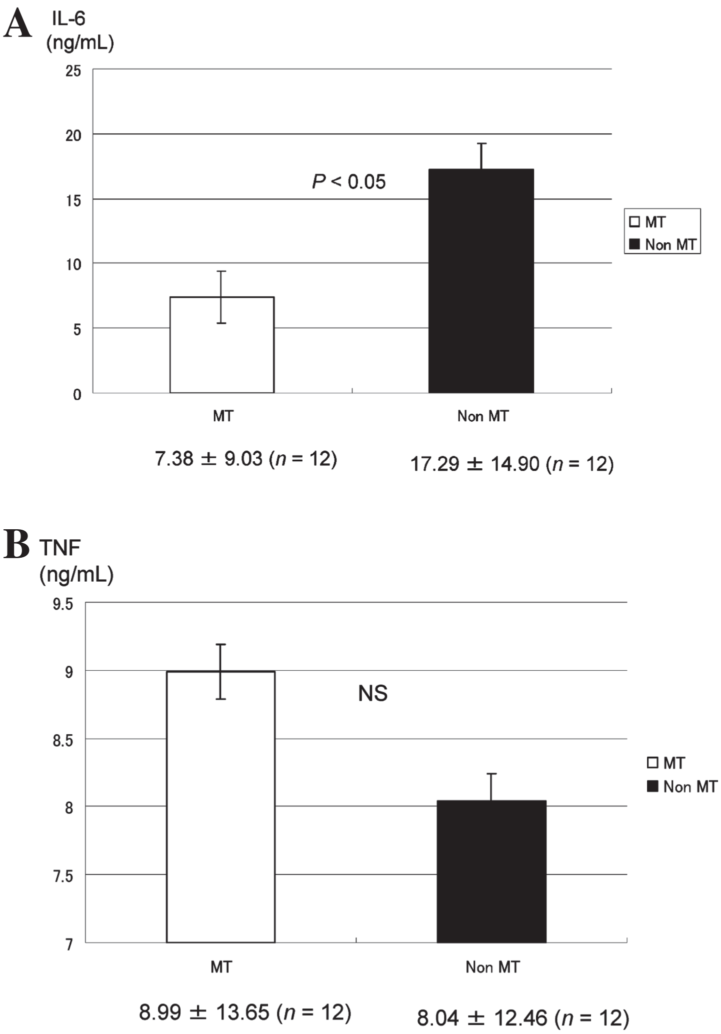

Figure 6. Levels of the plasma proinflammatory cytokines IL-6 (**A**) and TNF (**B**).

0.05, noradrenaline:. 315.08 ± 153.90 pg/mL versus 496.08 ± 344.89, $P < 0.01$).

Since CHF is the one of the most frequent causes of death in elderly people, we investigated acute heart failure events and also exacerbation rates of chronic CHF in both groups. Figure 8 shows the frequency of acute CHF events and exacerbations of chronic CHF during the follow-up period in our hospital in both groups. The incidences of both acute CHF events and acute exacerbations of chronic CHF were significantly lower in the MT group than in the non-MT group (10.9% versus 34.4%, $P < 0.05$).

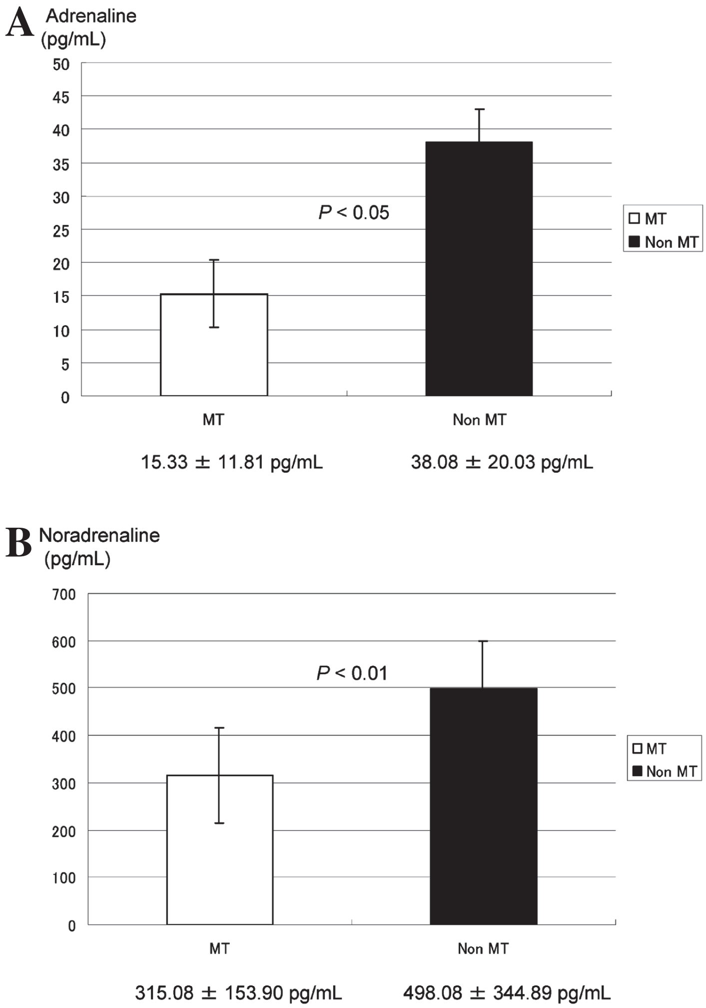

Figure 7. Plasma adrenaline (**A**) and noradrenaline (**B**) levels.

Discussion

The present findings suggest that the HRV parameters indicating parasympathetic activity were significantly increased and that those indicating sympathetic activity tended to decrease after MT. Plasma IL-6, adrenaline, and noradrenaline levels in the MT group were significantly lower than those in the non-MT group. Furthermore, the incidence of acute heart failure events and acute exacerbation of chronic CHF in the MT group were significantly lower than in the non-MT group.

Effects on HRV: Monitoring of HRV with an ambulatory Holter ECG system is currently widely used to assess autonomic functions in clinical cardiology.[27-31]

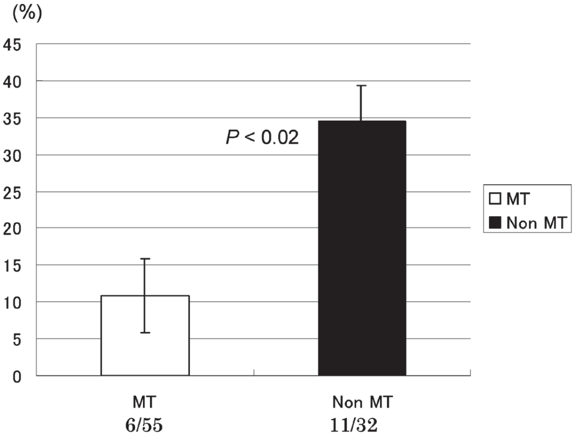

Figure 8. Incidence of CHF events between the MT group and non-MT group. The MT group (which received 45-minute MT sessions at least weekly for 10 months) had a significantly ($P < 0.05$) lower incidence of CHF events than the non-MT group. There were no significant differences between the two groups in terms of clinicodemographic findings, laboratory data, or grade of dementia.

It is generally considered the appropriate standard method for assessing quantitative markers of cardiac autonomic activity, as reported by a Task Force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology.[26)] It is also considered a useful method for predicting cardiac events such as microvolt level T-wave alternans.[32)] Recent advances in Holter ECG systems have produced equipment that is small and light -- such as the Fukuda-Denshi FD 50, which weighs only 40 g for the whole system -- and is therefore appropriate for prolonged measurement. Using this system, we could measure HRV in elderly dementia patients without distressing them. Currently, there are two major categories of HRV measurements: time domain and frequency domain. Time domain measures can be derived from: 1) direct measurements of normal-to-normal (NN) intervals (ie, intervals between adjacent QRS complexes caused by sinus depolarization) or instantaneous heart rate; or 2) the differences between NN intervals.[26)] Although it is generally preferred to measure time domain parameters from at least 18 hours of analyzable ECG data,[26)] we measured HRV for about 5 hours in the present study. We therefore used the maximum entropy method calculation (Mem Calc) incorporated in Chiram software[27)] for evaluating autonomic function in this study, because this system could analyze both spectral and time domains of HRV from 5-minute ECG segments using the exponential method of power spectral density analysis. Recently, Mem Calc has become popular as a method of assessing cardiac autonomic function.

In the present study, we found that both rMSSD and pNN50 (the two time domain parameters that we used) and HF spectra (the main frequency domain parameter that we used) increased significantly during MT, whereas the LF: HF ratio (the main sympathetic parameter that we used) did not change remarkably during MT, even in these elderly patients with cerebral vascular disease and dementia. Our previous study also yielded similar results.[33] Participants who did not receive MT did not exhibit significant changes in these parameters over the same time period (from 10:00 to 15:00). This suggests that music activated parasympathetic tone and attenuated sympathetic tone, even in the present elderly CVD patients with dementia, probably due to psychophysiologic effects in which the rhythm and tempo of the music induced relaxation and distraction responses in the limbic and hypothalamic systems of the brain.

Effects on cytokines: IL-6 has been reported to have a central role in inflammation of myocardium due to aging, because inflammation involving IL-6 is a component of many age-related chronic heart diseases, which often cause disability.[18,19] Further, TNF is reportedly increased in elderly heart failure patients even without prior myocardial infarction, because heart failure in the elderly can be caused by chronic pulmonary inflammatory disease.[34,35] TNF is produced by activated macrophages in response to pathogens and other injurious stimuli, and amounts sufficient to mediate local and systemic inflammation might be produced in the elderly decompensated heart.[36] Since pulmonary infection and congestive heart failure were the main causes of death in our geriatric hospital and the referring residential facilities, we investigated IL-6 and TNF in this study. The term "geriatric syndrome" is used for a complex clinical syndrome characterized by heart failure and pneumonitis by dyspnea and subsequent fever. Progression of these conditions is thought to be mediated by elevated levels of proinflammatory cytokines and neurohormones and neurotransmitters such as adrenaline, noradrenaline, and angiotensin II, via the toxic effects they exert on the heart and the peripheral vasculature.[37] These mediators are capable of inducing functional and structural changes in the left ventricle; ie, remodeling via direct effects on cardiomyocyte biology and extracellular matrix composition and via indirect effects on the loading conditions under which the heart must function. Therefore, circulating levels of IL-6 are elevated in patients with heart failure, particularly those with cardiac dysfunction and edematous decompensation, which are frequently seen in elderly CHF patients. Blalock[38] suggested that the immune system functions as a 'sixth sense' that detects microbial invasion and produces molecules that relay this information to the brain. Thus, IL-6 and other immunological mediators can gain access to brain centers that are devoid of a blood-brain barrier in the circumventricular region. Indeed, the dorsal vagal complex, comprising the sensory nuclei of the solitary tract, the area postremi, and the dorsal motor nucleus of the vagus, responds to increased circulating amounts of IL-6, TNF and other cytokines such as IL-10 by altering motor activity in the vagus nerve.[39] Activation of parasympathetic tone by soothing music might accordingly affect the hypothalamus by enhancing vagal activity following suppression of mainly IL-6 rather than TNF in this study. These facts could be explained by the physical conditions of the present patients, who were mostly in stable physical conditions, with the exceptions of a few episodes of CHF. Elevation of TNF might be seen in inflammatory processes such as fever, swelling pain, and or extensive atherosclerosis because TNF expression is up-regulated in inflammatory environments and atherosclerotic plaque that released plaque might cause acute coronary events.

Effects on catecholamines and CHF events: CHF is the most frequent cause of death and disability in the elderly, and it is common for elderly people to develop multiple cardiovascular disorders. In our hospital, between 60 and 70% of patients have CHF, and this condition is the most frequent cause of death. Therefore, routine management of elderly patients in geriatric hospitals should involve treatment and care designed to prevent CHF. CVD in elderly patients is commonly preceded by atherosclerotic changes in the coronary arteries. Advancing age is associated with increasing incidence of pulmonary infections, which can alter diastolic properties. In general, approximately one-third of patients with CHF have predominantly diastolic heart failure, which may be defined as pulmonary venous congestion secondary to pulmonary infection.[40] This type of heart failure involves alterations in mechanical properties that usually lead to neurohormonal changes.[41] A complex series of neurohormonal changes occur as a consequence of two principal hemodynamic alterations caused by CHF: 1) reduction of cardiac output; and 2) elevation of atrial pressure.[42] Many of these hemodynamic and neurohormonal changes reduce vascular compliance secondary to the systemic stimulation caused by adrenergic drive, activation of the renin-angiotensin-aldosterone axis, and augmented release of vasopressin and endothelin (which both act to maintain perfusion to vital organs and expand a reduced arterial blood volume).[43] In patients with CHF, the increased blood volume and decreased cardiac ventricular contraction reduce the baroreflex sensitivity. Volume loading usually accompanies the increases in cardiac pressures and dimensions that affect cardiac vagal afferent activity and sympathetic fiber endings.[44] In most mammals, the cardiac chambers project afferent fibers to the brain stem (vagal fibers) and the thoracic segments of the spinal cord (sympathetic fibers).[45] Reflex responses mediated by vagal cardiac afferents are influenced by various mechanical and chemical factors.[46] Although the physiologic role of these dual afferent innervations (sympathetic and vagal) has been the subject of intense controversy, most researchers believe that the vagal afferents are primarily involved in neurohormonal regulation of body fluid volume and that the sympathetic afferents are mainly involved in perception of cardiac pain.[47,48] These neurohormonal regulatory mechanisms decrease adrenaline and noradrenaline reuptake in the failing heart, in which there are increased catecholamine plasma levels secondary to the reduced noradrenaline spillover rate.[49] Thus, increased catecholamine release might contribute to further elevation of cardiac catecholamine levels in aging patients.[50] Soothing music can decrease the severity of sympathetic activation states such as anxiety, tachycardia, and tachypnea, via vagal innervations. This vagal activation by MT appears to protect against CHF events by reducing both adrenaline and noradrenaline levels. This could explain why patients in the present study who received 45-minute MT sessions at least weekly for 10 months had a significantly lower incidence of CHF events than patients with a similar background who did not receive MT (Table I, Figure 8). Research suggests that such vagal activation protects against CHF in elderly patients with CVD by antagonizing sympathetic nervous activation in the heart.

However, the present study has several limitations. First, patients were not properly randomized at the time of admission. Second, CHF was diagnosed according to chest X-ray findings and subjective symptoms (NYHA classification); we did not measure biochemical indicators of CHF such as BNP[24] and we did not perform echocardiography or radionuclide studies. Third, we could measure plasma cytokine and catecholamine levels in only a limited number of patients. Despite this limitation, we clearly demonstrated that IL-6, adrenaline, and noradrenaline levels were lower in the MT group than the non-MT group. We can conclude that soothing music might have a beneficial effect on vagal-cardiac motor neuron activity in CHF patients despite aging and dementia.

Conclusion: The evidence discussed in the present article suggests that music can enhance parasympathetic activity, even in very elderly patients with CVD and dementia. This enhancement of parasympathetic tone by music could result in decreased plasma levels of IL-6, TNF, adrenaline, and noradrenaline. Hence, by altering autonomic activity, MT may help improve cardiovascular status in patients with CHF. Thus, it appears that MT is useful in promoting the stability of elderly CVD patients with dementia. We conclude that MT might be a useful and inexpensive method for the prevention of CHF events in elderly CVD patients and could contribute to economically efficient health management as our society continues to age.

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