Letter to the Editor

A potential linkage between mitochondrial function of the heart and leg muscles in patients with heart failure

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Heart failure (HF) is a chronic and devastating illness becoming an increasingly important burden on the health care system. Reduced exercise tolerance is an independent predictor of hospital readmission and mortality in patients with HF [1], and is thought to be a therapeutic target [2]. Although central factors such as ejection fraction (EF) or cardiac output do play a role, peripheral factors which include reduced skeletal muscle, an alteration in fiber type to one with less oxidative properties, and decreased ATP production, are mainly responsible for the reduction in exercise capacity [3]. From these findings, mitochondrial function is thought to be an important factor in the skeletal muscle in HF patients.

We recently reported that the retention of Technetium-99m sestamibi (99mTc-MIBI) correlated inversely with mitochondrial function in vivo and ex vivo in various organs [4]. 99mTc-MIBI is a lipophilic cation used for the clinical diagnosis of coronary artery disease. 99mTc-MIBI is transported to the myocardium via coronary blood flow, where it is rapidly incorporated into myocardial cells by diffusion, and binds to mitochondria [4,5]. In clinical settings, the MIBI washout rate increased if mitochondrial dysfunction was present in HF patients [6]. Moreover, we and other groups demonstrated that mitochondrial functional assessment by 99mTc-MIBI was not organ-specific including the skeletal muscle [4,7,8].

To gain insight into the mechanisms underlying exercise intolerance in HF, we analyzed 99mTc-MIBI washout of the heart and leg muscles along with other clinical and cardiopulmonary exercise (CPX) parameters.

We studied 45 consecutive hospitalized patients with CHF treated for acute decompensation. CHF was defined by the Framingham criteria. Written informed consent was obtained from all patients, and the study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board of Kitano Hospital. The exclusion criteria consisted of Killip class IV HF at the time of the study, acute myocardial infarction, and no consent. Echocardiographic data, levels of brain natriuretic peptide (BNP), the estimated glomerular filtration rate, C-reactive protein levels, and medical history were analyzed. A dose of 740 MBq (20 mCi) of 99mTc-MIBI was administered intravenously under resting conditions after an overnight fast. Planar images followed by single photon emission computed tomography images were obtained 20 min and 3 h after the injection for the calculation of the washout rate (Supplementary materials) [6].

All data are expressed as the mean ± standard deviation (SD). Differences between groups were compared using the Mann-Whitney U-test. The correlation analysis was carried out using the Pearson’s product-moment. A multiple general linear model in Poisson distribution by the likelihood-ratio chi-square test was used when the determinants of parameters were analyzed. In all tests, a value of p < 0.05 was considered significant.

Patient characteristics were as follows: 62% were male; 37% had dilated cardiomyopathy; 55% had hypertension; 24% had diabetes; the mean age was 68 years; the mean EF was 41%; the mean BNP level was 370 pg/ml; and the mean washout rate of the heart and the leg muscles was 46% and 30%, respectively. See details in Supplementary Table 1.

Fig. 1A and B show multiple scatter plots and correlation coefficient, respectively, of the variables. The 99mTc-MIBI washout of the heart and BNP and the washout of the heart and leg muscles were focused in Fig. 1C and D, respectively. A higher washout rate represents mitochondrial dysfunction. The washout rate of the heart inversely correlated to BNP level increase (Fig. 1C). 99mTc-MIBI washout rate of the heart positively correlated with the washout rate of the leg muscles (Fig. 1D), but not with left ventricular EF (Fig. 1A, pink circle). In multivariate regression analyses (Supplementary Table 2), the 99mTc-MIBI washout rate of the leg muscle and BNP levels were the factors that determined the washout rate of the heart.
Fig. 1. Association between the MIBI washout rate of the heart and leg muscles (A). Multiple scatter plots of the variables. A red circle focused in panel C. A purple circle focused in panel D. A pink circle indicated the relationship between \(^{99}\text{Tc}\)-MIBI washout rate of the heart and left ventricular ejection fraction. (B) Pearson’s correlation coefficient. (C) BNP levels and \(^{99}\text{Tc}\)-MIBI washout rate of the heart and (D) \(^{99}\text{Tc}\)-MIBI washout rate of the heart and leg muscles. Line, linear correlation with standard deviation.

Fig. 2. Association between the CPX parameters and the MIBI washout rate of the heart and leg muscles (A). Multiple scatter plots of the variables. (B) Peak oxygen consumption and \(^{99}\text{Tc}\)-MIBI washout rate of the leg muscles. Line, linear correlation with standard deviation.
We analyzed data obtained from 22 patients who underwent CPX. Patients who underwent CPX were younger, but the other parameters were not significantly different from those who did not undergo CPX (Supplementary Fig. 2 and Table 3). PeakVO₂ was negatively correlated with the ⁹⁹mTc-MIBI washout of the leg muscles and weakly positively correlated with the length of the circumflex of the thigh (Fig. 2A). Fig. 2B shows the relationship between peak oxygen consumption and ⁹⁹mTc-MIBI washout of the leg muscles. Determinants of peak oxygen consumption in the subgroup were the ⁹⁹mTc-MIBI washout of the leg and EF. Multi-collinearity was observed between the ⁹⁹mTc-MIBI washout of the heart and leg muscles and the length of the circumflex of the thigh (Supplementary Table 4).

The factors linking the heart and the leg muscle are currently unknown. Mechanisms involving sympathetic neural activation; cellular metabolism in the cardiac and skeletal muscles; inter-organ relationships such as anemia, chronic kidney disease, liver congestion, and depression; and inflammatory cytokines may contribute to the linkage between mitochondrial function of the heart and peripheral muscles in HF patients [9]. Brain-derived neurotrophic factor is involved in depression and is decreased in HF patients. It regulates skeletal muscle energy metabolism and is one of the linking factor candidates [10].

Muscle mass (i.e., circumflex of the thigh), in addition to the mitochondrial function of the legs, is the deciding factor for exercise capacity. In fact, a reduction in mitochondrial function and the inability to utilize oxygen delivered, i.e. low peripheral O₂ extraction may contribute to the reduction in oxidative capacity. Thus, possible targets for exercise interventions to improve exercise intolerance in HF are not only the muscle’s mass but also the quality of the skeletal muscle [3].

There are several limitations. First, CPX was not done in all patients, and there were no CPX values in healthy controls. Second, we could not assess other markers of mitochondrial function or morphology of the heart and skeletal muscles as such analysis requires biopsy samples, which is beyond the scope of the study.

In summary, we demonstrated a clear correlation of mitochondrial function between the heart and skeletal muscles and biomarkers of HF. Our results indicate that mitochondrial function of the leg muscle, along with the muscle volume, may limit exercise capacity in patients with CHF.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.04.049.

References


Conflict of interest

There are no disclosures to declare.