中文題目：藉非侵襲性心臟超音波診斷之 dasatinib 引發之可逆性肺動脈高壓
英文題目： Reversible dasatinib-related pulmonary arterial hypertension diagnosed by noninvasive echocardiography

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Background: Pulmonary arterial hypertension (PAH) is an uncommon adverse effect of tyrosine kinase inhibitor. The article by Montani et al. demonstrated PAH in patients treated with dasatinib. We report a 33-year-old male with chronic myeloid leukemia suffered from short of breath after 63-month-use dasatinib. Noninvasive echocardiographic assessment revealed reversible PAH corresponding to clinical manifestation.

Case presentation: A 33-year-old male with chronic myeloid leukemia presented with progressive dyspnea on exertion in October 2013. He was known to have chronic phase chronic myeloid leukemia since January 1998. The initial laboratory data reveals eosinophilia, basophilia, low leukocyte alkaline phosphatase score, and positive BCR-ABL gene. He was initially treated with hydroxyurea 1000mg twice per day, and then commenced imatinib at 800mg/day since May 2002.
Under imatinib use, hematological complete remission was achieved, but there is no cytogenetic remission with positive b2a2 BCR-ABL mutation. Point mutation in kinase domain of BCR-ABL with F359V was identified. Imatinib was shifted to dasatinib 100mg/day in July 2008 and major molecular response was achieved. However, he suffered from progressive dyspnea in October 2013. The auscultation showed bilateral clear breathing sound. Prominence of bilateral hilar shadows was present on chest plain film (figure 1A). No thromboembolism evidence existed but dilatation of pulmonary trunk and proximal arteries in chest Computed Tomography scan was found (figure 1B). Tc-99m DTPA aerosol ventilation and Tc-99m MMA perfusion scintigraphy reveals V/Q match reduction of pulmonary functional volume. Doppler transthoracic echocardiography shows severe pulmonary arterial hypertension with estimated pulmonary artery systolic pressure (PASP) 105mmHg, right atrial and right ventricular dilatation, and severe tricuspid regurgitation (figure 1C and 1D). We stop using dasatinib but the symptoms persisted. One month later, we added on phosphodiesterase type 5 (PDE 5) inhibitor, sildenafil, and the symptoms improved gradually. We followed echocardiography three months later and estimated PASP regressed back to 45mmHg (figure 1E). Dasatinib was replaced by nilotinib in this patient.

Discussion: Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure (PAP) of > 25 mmHg at rest, or > 30 mmHg during exercise. The definite diagnosis includes invasive right heart catheterization. However, there is good correlation between transthoracic echocardiography and right heart

catheterization measurement of PASP. PAH is suspected if noninvasive PASP, determined by tricuspid regurgitation peak gradient (TRPG) and right atrial pressure(RAP) according to the simplified Bernoulli equation, is >35mmHg measured by Doppler transthoracic echocardiography.

Since 2007, the report from Quintás-Cardama et al. suggested the association between dasatinib and pulmonary hypertension. 9 cases of symptomatic pulmonary hypertension treated with dasatinib have been identified definitely in 2012. PAH appears as late complication of dasatinib, occurring after 8 to 48 months of exposure. The possible mechanism is dasatinib served as multi tyrosine kinase inhibitors, including BCR-ABL, SRC, c-kit, and PDGFR. Symptoms are improved after discontinuation of dasatinib in majority of cases, but some cases require PAH-specific therapy with sildenafil. In summary, we reported a typical case of dasatinib-induced PAH diagnosed by noninvasive echocardiography.

Figure 1.