High altitude exposure results in hypoxic pulmonary vasoconstriction (HPV) and increased pulmonary pressure. This study examined the relationship between acute changes in resting pulmonary pressure and gas-exchange measures during exercise in a group of non-acclimatized climbers summiting Mount Kilimanjaro. Twenty-seven climbers (age, 44 ± 15 years) completed the study. Exercise testing (4-min step test with gas-exchange) and echocardiographic measurements were completed at four different altitudes: 8801 m (barometric pressure, PB = 690 mmHg); 3500 m (PB = 505 mmHg); 4600 m (PB = 428 mmHg) and on return to 880 m (8802 m). Right ventricular systolic pressure (RVSP, mmHg) progressively increased as PB fell during the ascent (8801 m: 19 ± 4; 3500 m: 27 ± 8; 4600 m: 33 ± 7 mmHg). During exercise, the fall in PB was associated with a decrease (P < 0.01) in oxygen saturation (nadir SpO2(%): 8801 m: 96 ± 2; 3500 m: 82 ± 3; 4600 m: 73 ± 4). The time-course changes in gas exchange tracked changes in RVSP during ascent with a progressive decrease (P < 0.01) in SpO2 and end tidal carbon dioxide production (end-exercise PETCO2, mmHg: 8801 m: 37.1 ± 3.6; 3500 m: 28.5 ± 2.6; 4600 m: 20.8 ± 1.9) and an increase in breathing efficiency (VE/VCO2: 8801 m: 28.5 ± 2.9; 3500 m: 35.8 ± 4.6; 4600 m: 50.7 ± 5.8). However, while SpO2 and RVSP normalized on return to lower altitude (8802 m), gas-exchange measures remained altered (PETCO2, mmHg: 31.2 ± 3.0; VE/VCO2: 32.8 ± 3.2, P < 0.01 versus 8801 m). With high altitude exposure, there is an increased ventilatory drive characterized by altered gas exchange and associated changes in SO2 and pulmonary pressures. However, following high altitude exposure and once SpO2 and pulmonary pressures are normalized, gas-exchange measures remain altered suggesting that HPV is no longer a potential stimulus for an increased ventilatory drive.