SUPPLEMENTARY DATA

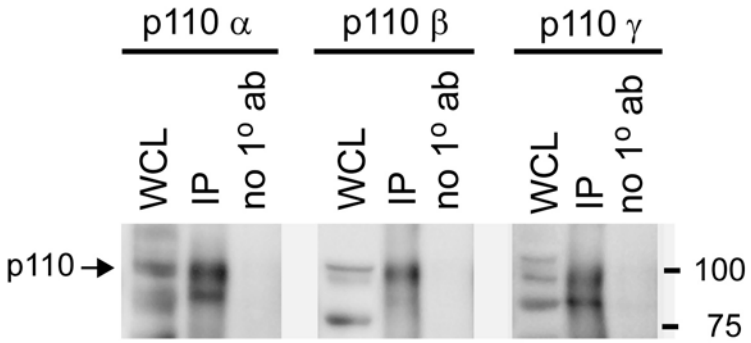

Fig. S1. PI3K subunits p110α, β and γ were immunoprecipitated from guinea pig ventricular myocyte lysates using isoform-specific antibodies and subjected to Western blot analysis. Shown are whole cell lysates (WCL), corresponding immunoprecipitates (IP) and negative controls with no primary antibody added (no 1° ab). P110 immunocomplexes immobilized on protein-G beads were used for isoform-specfic measurement of cardiac phosphoinositol 3-kinase activity as described.

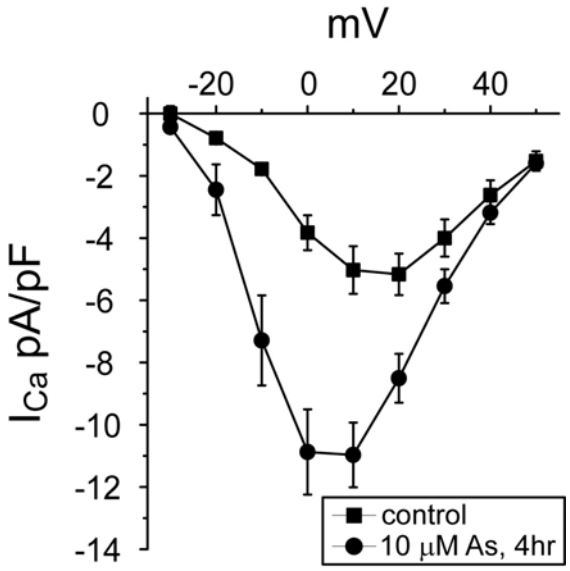

Fig. S2. As_2O_3 increases cardiac calcium currents on short-term incubation. Calcium current traces were elicited as described in Fig.1. Shown are averaged I-V relationships measured under control conditions and following a 4hr incubation with 10μM As_2O_3 (n=5-6).

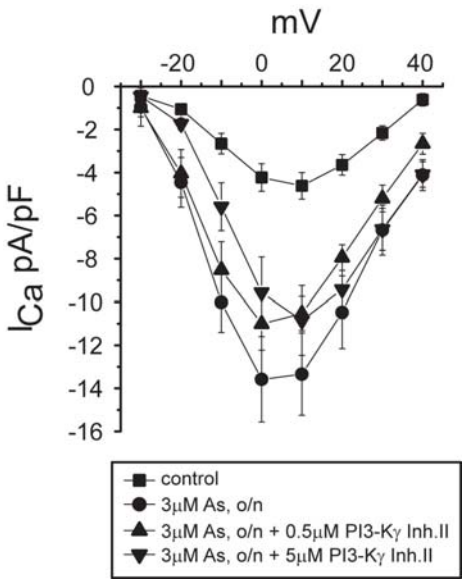

Fig. S3. As_2O_3-induced increases in cardiac calcium currents are not blocked by PI3-Kγ Inhibitor II. Calcium current traces were elicited as described in Fig.1. Shown are averaged I-V relationships measured under control conditions, following overnight incubation with 3μM As_2O_3, and following a 90 min incubation with either 0.5 or 5μM PI3-Kγ Inhibitor II in myocytes pretreated overnight with 3μM As_2O_3 (n=5-7).

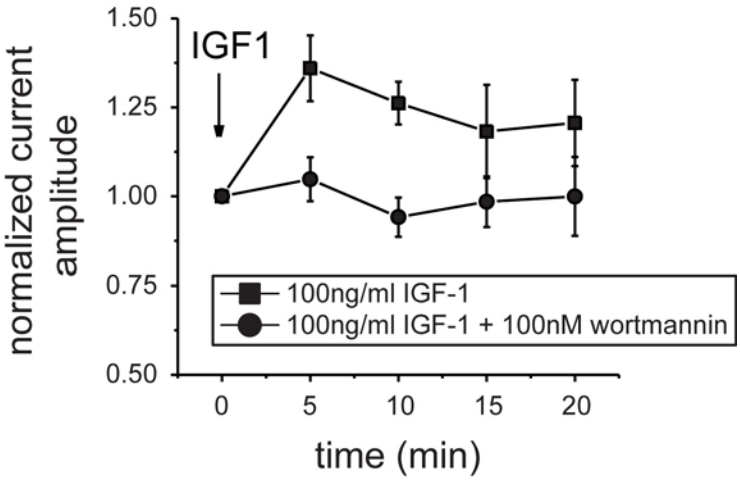

Fig. S4. Acute application of 100ng/ml IGF-1 increases cardiac calcium currents in freshly isolated guinea pig ventricular myocytes. Shown are normalized current densities elicited with a depolarizing test pulse to +10 mV (HP= -40mV). Recordings were performed in the perforated patch configuration. IGF-1 induced current increases are blocked by 100 nM wortmannin (n=3-4).

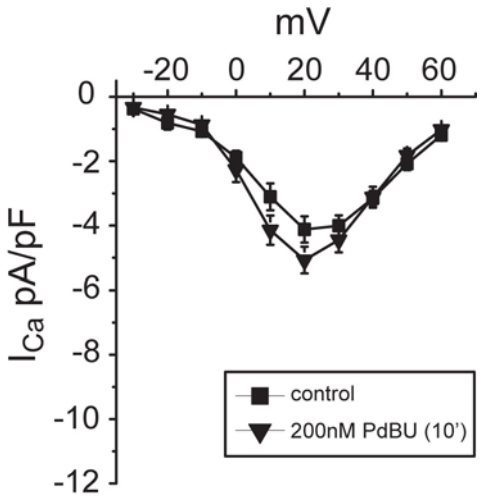

Fig. S5. Effects of phorbolester PdBU on cardiac calcium currents. Shown are averaged I-V relationships recorded under control conditions or following acute application of 200nM PdBU. I-V relationships in the presence of PdBU were recorded 10 min after start of drug application (n=5-11).

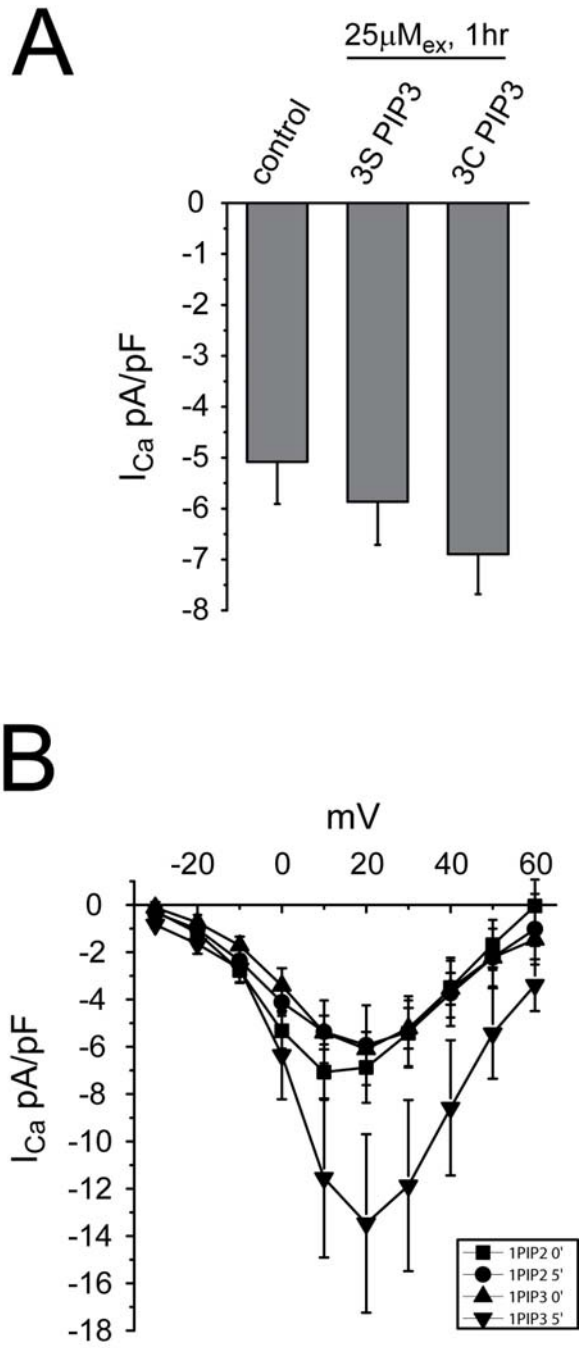

Fig. S6. PIP3 effects on cardiac calcium currents. A, maximal calcium current densities measured in cardiomyocytes using perforated patch recordings under control conditions or following a 1 hr pre-incubation with 25μM of the metabolically stabilized PIP3 derivatives 3S- and 3C-PIP3 (n=6). B, shown are averaged I-V-relationships measured in cardiomyocytes on internal perfusion with either 1μM C8-PIP3 or C8-PIP2 following overnight incubation with 1μM As_2O_3. I-V relationships were recorded immediately (0') or 5min (5') after gaining whole cell access (n=5).

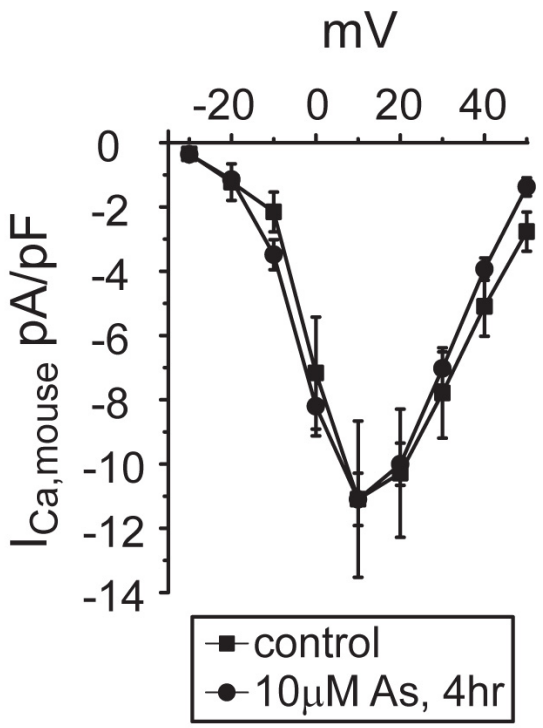

Fig. S7. As_2O_3 does not increase cardiac L-type calcium currents in mouse ventricular myocytes on short-term incubation. In mouse cardiomyocytes it has been shown that muscle-specific knock-out of PTEN results in a modest increase in calcium current density of about 30-35%. Given that we report oxidation of only about 30% of total PTEN on exposure to As_2O_3, we reasoned that in wildtype mice changes of L-type calcium currents should be very small (in the range of about 10%) on exposure to As_2O_3. To test this hypothesis we exposed 'wildtype' mouse ventricular myocytes for 4hr to 10 μM As_2O_3. In these experiments calcium current traces were elicited using 300ms step depolarizations in increments of 10mV from -30 to + 50mV (hp -40mV) under control conditions or in the presence of As_2O_3 (protocol is identical to the one used in guinea pig experiments). Depicted are averaged I-V relationships measured under control conditions and following 4hr drug exposure (n=7). As can be seen from IV-relationships, in mouse myocytes calcium current densities were not increased on incubation with As_2O_3. Here, it is also important to note, that calcium current densities in mouse myocytes measured under control conditions are significantly larger than corresponding current densities measured in guinea pig ventricular myocytes (-11pA/pF versus -4.6pA/pF).