Outflow tract defects account for around 30% of all congenital heart disease and are associated with a significant health burden and ongoing late mortality despite complete repair. Although outflow tract defects manifest as a range of anatomically distinct and apparently heterogeneous lesions – tetralogy of Fallot, double-outlet right ventricle, interrupted aortic arch, transposition of great arteries, truncus arteriosus, and other related defects – embryologically they appear to have a common origin related to abnormal development of the embryonic conotruncus during the septation of the arterial outflow tract. In the vast majority of cases (80%), the genetic etiology is not known. The most common defect causing outflow tract defects is the 22q11del that only accounts for 10–15% of cases overall.

In the past decade, major advances using mouse models have created a paradigm shift in our understanding of cardiac development through the discovery of the second heart field. While the primary heart field gives rise to the left ventricle and most other cardiac structures, the right ventricle and the outflow tract arise from the embryologically distinct second heart field. Proliferation and differentiation of the second heart field are controlled by a complex transcriptional network. Pioneering work in the understanding of the second heart field including lineage-tracing studies has shown that perturbations in genes of the second heart field result in abnormal formation and septation of the arterial outflow tract resulting in outflow tract defects. Computer-assisted 3D reconstruction analysis to assess spatial and...
developmental gene expression patterns, morphogenesis, and proliferation in situ has further helped understand outflow tract morphogenesis and effect of dysregulation of genes regulating its development.

The foregoing chapters discuss the history of the second heart field, the central role of multipotent second heart field progenitors in cardiac development and their contribution to the definitive arterial pole, the major signaling pathways that control second heart field progenitors including the role of genes like Mef2c, Cadm4, and Foxc2, as well as the environmental factors in outflow tract defect development. Eventually, knowledge gained from these model organisms can be used to guide genetic screening of human subjects to identify causal genes associated with outflow tract defects in humans.